CHAPTER XIV-A

FIBROSITIS

By WALTER I STEINER

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Definition — Fibrositis is an acute subacute or chronic disease characterized by a non suppurative inflammation of fibrous tissue the connecting tissue framework of the body As this tissue consequently is very widespread it may be seen in many different locations

If seen in the fibrous tissue of the muscles and tendons of the neck it is known as *cephalgia* nodular or indurative headache if in the fibrous tissue of the sterno-cleido muscles *torticollis* if in the fibrous tissue of the muscles of the pleura *pleurodynia* if in the intramuscular fibrous tissues elsewhere *myositis myofibrositis* or better *fibrositis* if in the intramuscular fibrous tissues of the lower back *lumbago* (of the fibrositis variety) if in the periarticular fibrous tissues *capsulitis* if in the bursal fibrous tissues *bursitis* if in the subcutaneous tissues *panniculitis* if in the perineural fibrous tissues *sciatica* or *brachialgia* if in the fibrous tendinous tissues located in the palms of the hands *Dupuytren s contractions* It may be seen also in the secondary forms in both gonorrhea and gout in the fibrous plantar tissues of the feet leading at times to the formation of nodules It is met with likewise in this variety in rheumatism atrophic arthritis and other conditions In short it may be seen in the ligaments tendons muscle sheaths fascia aponeuroses periosteum nerve sheaths or any part of the body where fibrous tissue is found The disease has been little known in this country until recent years William Balfour of Edinburgh (1816) first described the definite fibrous thickenings to which Froriep (1843) later drew attention English and

Swedish observers have written mostly upon it During the World War the condition was wrongly designated as myalgia for the intramuscular fascia and not the muscle fibers themselves are concerned The term fibrositis was first coined by Sir William Gowers in 1904

Etiology

Bacterial or metabolic toxins are said to be at fault or there is a bacterial invasion of the blood stream Trauma especially from long continued strain cold dampness and fatigue are said to be exciting factors in the formation of this malady as well as the persistent overuse of muscles Stockman thinks that the condition is due to small colonies of microbes which invade the tissues and cause a reaction which comparatively rapidly destroys the invaders which are non pyogenic and consequently do not attract the polymorphonuclear leukocytes Hence it produces no softening of the tissues or pus formation but leaves behind instead a small patch of inflamed fibrous tissue which persists and spreads He considers that the frequent relapses and exacerbations which many patients are subject to as well as the gradual spread of the disease suggest a chronic general infection by organisms which irritate by their toxins but are of very attenuative virulence It is possible Stockman continues that the frequent exacerbations and tendency to spread are due to other irritating causes such as constant recurring exposure to cold and damp Prolonged search always has failed to reveal any organisms in the inflamed tissues and cultures therefrom invariably have proved sterile

Specific hypersensitivity inherited or acquired must be regarded as an etiological factor of importance although there are many gaps in our knowledge of how this is brought about (Buckley)

Pathology

In the earliest lesions we find in the implicated areas swellings due to serofibrinous exudate which are gradually partly absorbed many fibroblasts are next observed leading later to the formation of new fibrous tissue The walls of the arterioles are thickened and show evidence of an interstitial inflammation as well as the nerve filaments Still later the inflammation partly disappears and dense fibrous tissue which is either general or local can be noted now If local it forms nodules varying in size from a grain of wheat to that of a bean and may be felt locally either deep in the muscles or between them after the acute stage of the in

flammation has subsided The nodules frequently are very tender on palpation The common locations are in the lumbar region chest hips fascia lata calves trapezius deltoid intercostal pectoral and rectus abdominis muscles and the soles of the feet The pathology has been studied chiefly by Stockman and Schmidt who appear to have been the chief ones to excise bits of tissue for investigation The degenerative aspect of fibrositis is seen in later years as fibrosis at which time the signs of inflammation have entirely disappeared

Symptoms

The symptoms are chiefly local and not constitutional They may come on after a few hours incubation continue a few days or become chronic in character *The constitutional disturbances generally are slight* and even in very severe cases there may be no fever The chief symptoms are pain and stiffness The pain resulting from swelling of the tissues when tightly bound is due to a compression of nerve endings especially in their passage through bony canals or where their roots emerge from the vertebral canal If the muscles lie between bones or tight fascial plains they may cause also a strain upon inflamed ligaments The pain may differ in character from a dull ache to a violent cramp like pain The sharp pain may last a few hours and later become a dull ache or it may continue as at onset for a long time It has a tendency to recur in either of its two types above mentioned The pain frequently is relieved by pressure Muscle fatigue after exercise is complained of early and is seen very frequently Adhesions may form later between adjacent muscle and tendons Fibrositis when seen in the hands on the back of the proximal phalangeal joints in the shape of soft pads is called Garrod s pads *after the London physician who first described them* They generally indicate the existence of fibrositis elsewhere and must be distinguished from rheumatoid arthritis which is possible by recognizing that the sedimentation rate of the former is normal The French have called an extreme *form of fibrositis* rhumatisme chronique fibreux or Jaccoud s disease where all the joints of the extremities are effected by extreme rigidity It may be related to scleroderma Pelvic fibrositis may be a common cause of dysmenorrhea and of pelvic pains

Prognosis

The outcome is very uncertain Early treatment and the age of the patient are the most important factors in the outlook of this disease for

younger patients frequently recover A tendency to recurrence should not be forgotten and also that the recurrence frequently is at the same place Damp weather and indiscretions in diet are concerned frequently Dupuytren s contraction rarely yields to treatment except in a few cases where surgery has been tried *successfully* *Periarticular fibrositis may* prove very refractory to treatment It is generally met with later in life and frequently leaves some disability Bursitis may be troublesome if adhesions form but in young subjects the recovery generally is complete Some think that constipation and colitis are of importance as causative factors They should if present require vigorous treatment and should be investigated at the onset of the treatment Infected foci also should be looked for The liability to recurrence and chronicity should be kept in mind

Diagnosis

Generally there will be no difficulty in diagnosing this condition The so-called cephalgia or indurative headache may be distinguished from migraine by its lack of constitutional symptoms If the fibrous tissue in the pleura is affected it may be distinguished from intercostal neuritis as the pain usually is less circumscribed and paroxysmal with the absence of tender points along the course of the nerve and from pleurisy by the absence of fever and a friction rub The panniculitis variety may be distinguished from appendicitis by the superficial character and general distribution of the tenderness of the affected parts The skin also has a hard brawny feel and nodules frequently may be palpated in it In the capsulitis variety a thickening of the capsule may be detected with rarely a nodule in the capsule while the joints frequently are movable and thus can be distinguished easily from arthritis In the perineural type the pain is located along the side or front of the leg rather than along the course of the sciatic nerve and the Achilles tendon jerk invariably is absent This type also is associated generally with the intramuscular and periarticular varieties In bursitis there is not only an inflammation of the subacromial bursa but the adjacent tendons and the capsules of the shoulder joints are concerned also The lumbago variety should be diagnosed with great care as in no disease is more careful investigation required in order that serious mistakes may be avoided It must be distinguished from (a) ischemic lumbago which is due to an intermittent claudication which causes pain on walking (b) static conditions due to faulty posture (c) abnormal anatomical variations in the vertebræ (d) lumbo sacral and (e) sacro iliac joint strains (f) pelvic disease in

which both sexes may likewise enter in the differential diagnosis but is readily ruled out as well as (g) a strain from trauma which does not cause accompanying fibrositis and (h) a neuritis of the posterior nerve roots which may cause more difficulty but should be distinguished readily

The nodules in fibrositis are less sharply outlined and blend more with the surrounding tissues than those seen in rheumatic fever and arthritis Besides the nodules in the latter two conditions are not painful on pressure

Treatment

The use of rest of the affected parts is of prime importance The treatment par excellence is by massage which should be given after the very acute symptoms have subsided and given by deep massage over a long period It is only thus that the nodules if they exist can be kneaded out Vaccines have been tried but generally with ill success and protein shock generally has been a failure The use of baths in spas often is most efficacious as well as heat in any form Counter irritants likewise may be useful Acetyl salicylic acid 0.6 gm (gr x) or sodium salicylate 0.6 to 1 gm (gr x-xv) frequently have proven beneficial as well as salol 0.3 gm (gr v) The wine of colchicum is useful in the gouty variety 1 cc (m xv) Potassium iodide may be used in chronic cases After the patients recover they should avoid exposure to cold and damp as much as possible

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CHAPTER XV

CHRONIC ARTHRITIS

By ROBERT T. MONROE

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Definition — Chronic arthritis is a persistent frequently progressive affection of the joints and their related structures Common usage defines it loosely as distress of any degree or character that is located in or referred to joints Rheumatism with the laity is a synonym

Somewhat discordant experiences with the disease are reported from different countries and from different localities in the same country Clinics and specialists in arthritis undoubtedly attract a disproportionately large number of the more severe and atypical cases General practitioners often find that descriptions drawn from such cases do not apply to many of the patients under their care Much has been done in recent years to harmonize the various points of view by the formation of societies devoted to the study of rheumatism Good reports are now issued annually in England* and the United States†

The Anatomy and Physiology of Joints

These are subjects which have been somewhat neglected until recently and our knowledge of important facts still is seriously deficient A few brief notes of current ideas may therefore be in order

A joint is a group of structures which attach bones together It consists essentially of two bone ends in apposition cushioned by cartilage sealed by a capsule lined by synovial membrane and held in place by ligaments and muscles Differences in functional requirements and in location in the body naturally result in a great variation in the appearance relative importance and cellular constitution of each of these component parts

Bone is living active tissue Its health is essential to joints If weight bearing lines are disordered or if structural changes occur the apposition of the bone ends may be imperfect and pain and disability may ensue It appears too that the marrow at the epiphyseal ends is vulnerable to infection for it is rich in blood vessels in which the circulation is sluggish Organisms in the blood stream may lodge there easily In growing bones the epiphysis interposes a barrier of fair strength to the passage of infection in either direction Thus osteomyelitis which arises in the

* Reports on Chronic Rheumatic Diseases Annual Report of the British Committee on Chronic Rheumatic Diseases appointed by the Royal College of Physicians C W Buckley Editor The MacMillan Co New York No I 1936 No 2 1936 No 3 1937 No 4 1938

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shaft often fails to penetrate beyond it and infection distally is limited by it so that epiphysitis presents a clinical picture which can be distinguished from osteomyelitis When maturity is reached however this barrier is gone the marrow of the shaft then is continuous up to the cartilage Before that time comes the bone beyond the epiphysis may be thought of as included in the joint since the joint capsule is attached at that line Bone marrow contains only a few nerves probably only those which are found in the walls of its blood vessels hence it is relatively insensitive Periosteum contains many blood vessels lymphatics and nerves and can be exceedingly sensitive

Articular cartilage is a most amazing structure Studies of its metabolism have shown that it requires very little food That is fortunate for it possesses no arteries veins or lymphatics We are forced to speculate on synovial fluid and subchondral vessels as the source of the energy of this cartilage by some unrevealed distributing system It is almost totally unable to regenerate after injury for example a superficial scratch may remain visible for many months Yet this gristle provides for the bones an elastic cushion which thrives on constant and prolonged hard use

Hyaline articular cartilage grows in fetal life by proliferation of spindle shaped cells lying in flat rows on the inner side of the fibro vascular perichondrium As they are pushed toward the bone growing center of the epiphysis these cells become spherical irregularly spaced and surrounded with an increasing amount of intercellular material In the deepest half or third they again assume an orderly alignment in rows perpendicular to the surface Perhaps this triple layering of cells of different density and orientation accounts for the resiliency which it appears to be the sole function of cartilage to furnish The perichondrium disappears shortly after birth When a fibrous layer is found enveloping an articular surface later in life usually it is an inflammatory extension of the synovial membrane Cartilage continues to grow however probably by adding to the intercellular substance possibly by an increase in the number of the cells in the deeper layers The clear intercellular cement becomes cloudy as it reaches the deepest layers Calcium is deposited in it on a line which marks the end of the bone marrow cavity after osteogenesis ceases This line is heavily calcified and highly polished as degenerated cartilage is worn away in osteoarthritis

The joint capsule arises from the periosteum near the epiphyseal line and surrounds the joint Its outer coat of inelastic fibrous tissue varies in density and strength in different joints and in different parts of the same joint It is strengthened appropriately by folds tendons and

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muscles arteries veins lymphatics and nerves are plentiful Its inner coat begins on the border of the articular cartilage and occasionally extends a short distance over its surface for it blends with the fetal perichondrium then it spreads out to cover all the intra articular structures The two coats move somewhat independently being connected by loose areolar tissue except in areas of stress and strain, where it is bolstered by tough collagen and many fibers Fat tissue is present at times in abundance often forming clearly defined adipose pads The blood supply is fairly rich being derived from anastomosing arteries in the neighborhood of the joint and from the circulus articuli vasculosus of Hunter at the margin of the articular cartilage A fine but rich network of lymphatic vessels extends throughout no direct openings into the joint cavity have been demonstrated Sensory nerves from peripheral nerve trunks are rather abundant It is assumed that the blood vessels have their usual vasomotor nerves

The surface of the inner layer of the capsule which defines the joint cavity is called the synovial membrane Often it is so loosely knit that its superficial fibroblasts appear identical with those which are beneath indeed if they are detached they are replaced quickly by others coming to the top In other joints it is more highly organized and contains large endothelial cells The regenerative power of each type is great Large strips can be removed and a new membrane promptly forms which is entirely similar in appearance and function if no pathological state exists in the joint capsule or fluid

Synovial membrane is not always smooth Transitory folds appear as the joint is moved and permanent folds are common at the margins of the articular cartilage Here too villi are found most often Villi are tiny slender round or flat processes of synovial tissue containing blood vessels and even nerves They vary greatly in length and width and move like seaweed in the joint cavity Their mucus cells contribute mucin to the synovial fluid Under pathological conditions they may increase enormously

The cavity of a joint normally is little more than a potential one It is filled by synovial fluid This is a colorless watery lubricant and buffer whose chemical and physical properties suggest that it is a simple filtrate of the blood plasma most likely from subsynovial vessels There appears to be no secretory activity on the part of the synovial cells except such as contribute mucin nor do the lymphatic vessels contribute a detectable portion It contains a few hundred cells to the cubic millimeter of which the majority are phagocytes Red blood cells are absent or few in number The formation and disposal of synovial fluid is slug

gish at rest Circulation is accelerated by motion of the joint and then it is driven into the lymphatics of the capsule Its amount may be increased quickly by hyperemia of the synovial membrane A joint effusion results which is likely to contain more protein and fibrin than normally depending upon the cause of the inflammation Such an effusion is of course an ideal medium for further growth of connective tissue This may hinder resorption of the fluid if it blocks access to lymphatics for they alone appear to be capable of clearing the joint of such large molecules as proteins In such an event exercise of the joint is all the more necessary

Bursæ are structures which are entirely similar to synovial membrane in cell types and construction Those which are loosely formed may appear in connective tissue anywhere under the skin or in the muscles in response to pressure or friction Others more carefully fashioned are found regularly in relation to certain joints with which they often communicate The bursal cavity normally is lubricated by a slight amount of fluid filtered from vessels in the surrounding connective tissue Bursal effusions occur from the same causes as joint effusions They may be absorbed slowly and calcium may be deposited in the fluid and in the walls

Synovial membrane also lines many tendon sheaths and surrounds the cartilaginous parts over which tendons play

It must be recalled that cartilage capsule and synovial membrane all arise from undifferentiated connective tissue Certain factors pathogenic to them can therefore be assumed to be harmful to connective tissue elsewhere in the body such as in the skin subcutaneous tissues and muscles Metaplasia also is a feature of such simple tissue One may find cartilage or bone at times in a joint capsule Hyaline cartilage may degenerate to fibrocartilage or fibrous tissue or may become calcified Portions of synovial villi may break off and float freely in the joint cavity proliferating and even adding cartilage and calcium salts

Each joint is constructed to fit a particular situation and to perform a particular group of motions It follows that the symptoms signs and results of disease in them vary greatly The symmetrical involvement of joints in many cases of arthritis may be due in part to the similar structure and duties of the same joints on each side of the body

Classification of Arthritis

There is adequate excuse for the unsatisfactory state in which the classification of arthritis languishes when one considers the variegated

muscles arteries veins lymphatics and nerves are plentiful Its inner coat begins on the border of the articular cartilage and occasionally extends a short distance over its surface for it blends with the fetal perichondrium then it spreads out to cover all the intra articular structures The two coats move somewhat independently being connected by loose areolar tissue except in areas of stress and strain where it is bolstered by tough collagen and many fibers Fat tissue is present at times in abundance often forming clearly defined adipose pads The blood supply is fairly rich being derived from anastomosing arteries in *the neighborhood of the joint and from the circulus articuli vasculosus of* Hunter at the margin of the articular cartilage A fine but rich network of lymphatic vessels extends throughout no direct openings into the joint cavity have been demonstrated Sensory nerves from peripheral nerve trunks are rather abundant It is assumed that the blood vessels have their usual vasomotor nerves

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more common forms Tissue is not available for study in early and mild cases Routine autopsies do not include representative joints Experimental work with various arthropathic agents in animals however and a few observations on early human cases lead to a fairly well accepted series of events

Atrophic Type

The process probably originates in subchondral bone or the vascular attachments of the capsule but the earliest joint manifestations are to be found in the synovial membrane This becomes swollen pink or red Microscopically there is edema of the underlying connective tissue and engorgement of the blood vessels Soon new blood vessels may appear between which cells of various types wander granulocytes lymphocytes and macrophages depending upon the causal agent Activity may cease at this point or even earlier and full recovery follow How often this happens is unknown It is perhaps reasonable to surmise that it is a very frequent occurrence Unfortunately progression also is common

Specific pathogenic agents stamp their characteristic pattern such as those of tuberculosis syphilis and the pyogenic organisms In other cases persistent activity paints a different picture The synovial lining thickens throughout its whole extent It encroaches upon the surface of the articular cartilage which eventually it smothers with a blanket of connective tissue pannus The entire wall of the joint capsule now shows induration Bursae which communicate with the joint are involved The villi clustered chiefly on the edges of the joint increase in size Rarely they become huge so that great masses can be excavated at operation Microscopically proliferation of all connective tissue elements may be abundant and numbers of wandering cells fill the interstices There are collections sometimes around the blood vessels sometimes in other foci of lymphocytes macrophages plasma cells and occasionally giant cells Some authors find that these focal collections of lymphoid cells lend a very distinctive appearance to this chronic granulation tissue As the process waxes and wanes there is disintegration of synovial cells here contraction of scar tissue there and proliferation elsewhere so that the inflammatory mass comes to vary in density thickness and vascularity

Articular cartilage is attacked sooner or later in all but the mildest cases Grossly the first sign is a loss of luster and clarity The surface becomes cloudy bluish or red Connective tissue shrouds its top and infiltrates its base The attack may be arrested at any point tempo

patterns that can be woven by many pathogenic agents over a long period of time in structures which are alike and yet unlike No scheme has met general acceptance Old terms acquire different meanings New terms add confusion There is no agreement as to what conditions are to be considered Shall arthritis be said to include all possible joint diseases or shall those of known etiology be excluded? Is it wise to attempt to define many precise categories or shall there be ample mis cellaneous and mixed brackets?

The author of this chapter subscribes to the belief that all diseases which are related to joints are or can contribute to chronic arthritis and that at the present time the simplest classification is the best This can rest upon the basis of the structures which are chiefly involved Of the intra articular tissues synovia can react to any agent only by in flammation and cartilage only by degeneration The extra articular tissues often share in what is taking place inside the joints but perhaps just as often they show a certain independence Diseases of the synovia of a primary or major degree are variously called synovitis infectious arthritis proliferative or rheumatoid arthritis I prefer the term *atrophic arthritis* since it is more general and more descriptive of the atrophy and asthenia which are prominent characteristics of the patients Diseases of the cartilage are called traumatic degenerative or osteo arthritis or preferably *hypertrophic arthritis* in contrast to the first Diseases of the extra articular supporting tissues which appear to be distinct are called bursitis fibrositis or periarticular fibrositis With the passage of time hypertrophic changes may appear in cases of atrophic arthritis or in fectious changes may take place in hypertrophic joints and bursitis is added sooner or later No advantage seems to be gained by regrouping them then as mixed cases or arthritis deformans Nevertheless this transition is so frequent as to make one hesitate to speak of the forms of arthritis as permanently distinct entities Hence we shall discuss

1 The atrophic type
2 The hypertrophic type
3 The periarticular type

Pathology of Arthritis

We have a wealth of information about the abnormalities wrought by certain forms of diseases in joints which have been sufficiently interesting to investigate after death or which have been opened surgically in life But we have no assurance that the changes which have been described therein are what can be seen in all kinds of joint disease or even in the

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changes as in the joints but often in different degrees and at different times The inflammatory reaction may attack tendons and aponeuroses Repair may leave them shortened or lengthened The healed capsule also may show abnormal laxity or shrinkage These features naturally add to the difficulty of maintaining normal apposition of bone ends and hinder good function of the joints

Subcutaneous tissues farther from the joints at times are involved in *the same inflammatory process Rarely this may be the outstanding* feature of an individual case which finally looks like scleroderma when fibrous tissue contraction has compressed the joints and drawn the skin tightly over them Subcutaneous nodules or fibromata entirely similar to those seen in rheumatic fever are found in a variable fraction of cases They consist of mononuclear cells arranged about a central necrotic zone and surrounded by dense fibrous tissue

Atrophy of the muscles which move the affected joints sets in early in the great majority of cases and must be due in large part to the disuse prompted by pain and swelling However these muscles microscopically reveal infiltrations of fibrous connective tissue between their bundles and collections of lymphoid cells about their blood vessels so that they must be considered to share directly in the disease process The original muscle mass is restored only slowly Often an appreciable *loss is permanent even with good joint function Peripheral nerve sheaths* occasionally are involved with resultant sensory and motor disturbances in their distribution

Atrophy of the skin particularly over the diseased joints but also elsewhere is found almost invariably In very active cases the skin is hyperemic therefore warm In less active more chronic cases it is likely to be pale than from loss of connective tissue and fat and moist from vasomotor changes *An extreme case may show obliterative endarteritis* about the fingers and toes

Lymphatic glands in the region of the affected joints frequently are enlarged Enlargement of the spleen is not uncommon particularly in younger individuals

Visceral changes have been reported but are not common They are such as might be anticipated in any persistent wasting process Valvular heart lesions are found in a small number of cases Cases in which many organs and tissues are affected in addition to joints have been reported *under different titles such as chronic rheumatic fever or disseminated* lupus erythematosus There is reasonable doubt as to the relationship *of these to chronic arthritis discussed in this chapter*

rarily or permanently but there is a tendency under this double assault for cartilage to disintegrate in a spotty fashion and finally to disappear Microscopically there is only cellular destruction no infiltration of blood vessels and no wandering cells Healing processes appear early but make a poor showing at restoration of the original architecture Fibrocartilage replaces hyaline cartilage It may form distinct epichondral granulations Masses of cartilage may grow by a process of metaplasia in the joint capsule or synovial villi thus altering further the original contours Some of them may become bone These excrescences tend to be sharp jagged and irregularly situated on the opposed surfaces quite unlike the spur formation of the hypertrophic type True osteoarthritic changes may appear however if the joint becomes well enough to be used vigorously

Fibrous adhesions tend to form between the granulating surfaces where they are in contact with each other If they are not broken up by motion of the joint or if fluid does not aid in separating them they become united more firmly Bony trabeculae ultimately bridge the space that once was a joint and ankylosis is said to have taken place With motion and a buffering fluid however there may be opportunity for the scar tissue to organize and present a fairly avascular surface to its neighbor A mobile joint remains the bone ends being cushioned by connective tissue and fibrocartilage

Effusion into the joint cavity may appear promptly slowly or not at all The fluid shows many variations in amount and in cellular and chemical constitution It is sterile by ordinary culture methods except in frankly septic joints but this is not adequate proof that it was not caused by infectious agents It subsides very slowly if access to the subsynovial lymphatics is impeded

Atrophy of bone is a very early finding It is greatest in the area adjacent to cartilage and extends for a variable distance up the shaft Decalcification of disuse can account for only a small fraction of it, contrary to the usual opinion The subchondral marrow is red from increased vascularity and soft from loss of calcium Microscopically the cancellous spaces are widened Circular areas near the old epiphyseal line are revealed as punched out areas by radiography There are more than the normal number of connective tissue elements present and occasionally focal collections of lymphocytes can be found Some degree of atrophy is permanent the area being filled with adipose connective tissue There is little tendency to deposit calcium in repair even when the disease is arrested and good function is restored

The synovial lining of bursæ and tendon sheaths shows the same

changes as in the joints but often in different degrees and at different times. The inflammatory reaction may attack tendons and aponeuroses. Repair may leave them shortened or lengthened. The healed capsule also may show abnormal laxity or shrinkage. These features naturally add to the difficulty of maintaining normal apposition of bone ends and hinder good function of the joints.

Subcutaneous tissues farther from the joints at times are involved in the same inflammatory process. Rarely this may be the outstanding feature of an individual case, which finally looks like scleroderma when fibrous tissue contraction has compressed the joints and drawn the skin tightly over them. Subcutaneous nodules or fibromata, entirely similar to those seen in rheumatic fever, are found in a variable fraction of cases. They consist of mononuclear cells arranged about a central necrotic zone and surrounded by dense fibrous tissue.

Atrophy of the muscles which move the affected joints sets in early in the great majority of cases and must be due, in large part, to the disuse prompted by pain and swelling. However, these muscles microscopically reveal infiltrations of fibrous connective tissue between their bundles and collections of lymphoid cells about their blood vessels, so that they must be considered to share directly in the disease process. The original muscle mass is restored only slowly. Often an appreciable loss is permanent even with good joint function. Peripheral nerve sheaths occasionally are involved with resultant sensory and motor disturbances in their distribution.

Atrophy of the skin, particularly over the diseased joints but also elsewhere, is found almost invariably. In very active cases the skin is hyperemic, therefore warm. In less active, more chronic cases it is likely to be pale, thin from loss of connective tissue and fat, and moist from vasomotor changes. An extreme case may show obliterative endarteritis about the fingers and toes.

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Hypertrophic Type

The earliest change is seen in the cartilage as a loss of luster in the central superficial area The intercellular material degenerates loosening the cells whose frame work it formed and allowing them to fall into the joint cavity As the process continues the deeper cartilage cells arranged in perpendicular rows lose their ground substance also and split in columns This is described as fibrillation Areas subjected to pressure are most affected and trauma and excessive use accelerate the process Ultimately the bone end is laid bare Meanwhile at the edges where they are covered by synovia cartilage cells are required to bear more weight than they are accustomed to do when they degenerate they are not free to enter the joint cavity and regeneration is possible because of access to a good blood supply consequently they undergo a metaplasia into connective tissue fibrocartilage and finally bone In some such manner chondrophytes and osteophytes are formed They are smooth rounded and curved fringing the head of the bone shrouding it or falling away from it according to the particular circumstances of the joint

As the shocks of continued function are absorbed more and more directly by bone the subchondral bone becomes hardened Highly polished grooves are worn in lines of frequent contact Superficial pits mark the outlets of exposed Haversian canals Rarefaction is not a feature except such as can be explained on the basis of disuse and senility and this is to be found mostly toward the shaft Punched out areas are however not uncommon at the lateral joint margins Inflammatory reactions and cellular foci are not seen

The synovial membrane shows no change at all in the average case It does not spread over the cartilage Trauma may cause hemorrhage in areas of pressure laterally with subsequent inflammatory thickening but there is no infiltration of small round cells Villi may be bruised in the same fashion and when they are they may be stimulated to form cartilage and bone At unpredictable times one of these masses breaks off from its slender pedicle and rolls painfully between the joint surfaces as a joint mouse There is no obliteration of the joint cavity Ankylosis of course does not occur for its forerunner granulation tissue is absent Motion of the joint can however be restricted seriously by the interlocking of marginal osteophytes and occasionally as in the spine these spurs actually fuse

The synovial fluid usually is normal in amount and composition It is sterile always Effusions serous more often than bloody may result from blows or from twisting sprains They tend to subside rather quickly

because lymphatic drainage is accessible. Effusions about Heberden's nodes, the hypertrophic spurs in the terminal interphalangeal joints occur quite frequently and for no apparent reason.

The outer layers of the capsule show no inflammation. They are subject to unusual pull and torsion when cartilage is no longer present to maintain the original width of the joint. This accounts for many of the splits and fractures that are seen in the associated tendons and aponeuroses and for the deposits of calcium and bone along the lines of their attachment to periosteum. Hinging joints such as the shoulders are particularly apt to show such degeneration. In late cases the arteries in the capsule and synovial membrane show sclerotic changes.

Bursæ in the region of the joint and elsewhere are for the most part unaffected. They may share in a joint effusion and in the fibrosis and calcification which takes place in their surrounding tendons. Muscles also tend to maintain a normal appearance and function. Atrophy corresponds in degree and duration to disuse. There are no changes in skin, subcutaneous tissues or viscera that can be attributed to the arthritis.

The joint changes in chronic gout usually follow the pattern of hypertrophic arthritis, except that salts of uric acid are deposited in cartilage, capsule, synovia, bone and periarticular structures.

Periarticular Type

Diseases of the supporting tissues of joints which are distinct from the changes in them which have been described in the atrophic and hypertrophic types are not clearly defined. It is possible to doubt whether they are entirely independent unless one goes beyond the rheumatic group of affections to such unknown states as panniculitis, myositis, etc. For a long time it was taught that atrophic arthritis began in the periarticular tissues. Opinion has changed but they are still assigned an important share in the disease. There is nevertheless an extremely common group of conditions called bursitis and fibrositis which never show the joint changes of the atrophic type and which for a long time fail to show hypertrophic changes. They are therefore considered loosely as a separate group, periarticular fibrositis.

Simple bursitis may be found in subcutaneous tissues anywhere as a result of repeated trauma; it then resembles a deep blister. The bursæ in the region of joints may show the inflammatory changes of synovitis due to unidentified infections or toxins. Attacks may be single (acute), several or successive and in the same or in different bursæ. As chronicity

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ETIOLOGY

The Atrophic Type

Age — The majority of cases begin between the ages of 20 and 50 but *no time of life is spared except possibly the first year* Cases which start in early childhood are rare and they are wont to show striking enlargement of the spleen and lymph glands (Still's disease) Those in later childhood and adolescence may be difficult to distinguish from rheumatic fever In early adult life occur many of the cases of atrophic arthritis of the spine and others that resemble septic arthritis The typical indolent progressive case has its first bout of joint pain in the thirties and forties Original attacks are not common after fifty when they begin late in life usually they are superimposed upon hypertrophic joints In my series of 267 cases 3 per cent began before the age of 10 15 per cent between 11 and 20 24 per cent between 21 and 30 20 per cent between 31 and 40 25 per cent between 41 and 50 11 per cent between 51 and 60 and 2 per cent after 61 The oldest was 72 The average age of onset was 32 years

Sex — *Females are affected three times as often as males* This curious fact is one on which most observers here and abroad are in agreement Since the disparity is much less before puberty and after the menopause and since many cases start in close association with the menopause and others are made worse by menstrual difficulties speculation has been free as to the particular sex-disability that is responsible Tendencies to nutritional defects and hypochromic anemia are worthy of mention

Race — Negroes are reported to be affected less often with any kind of arthritis than white people Some clinics treat an unusual number of individuals of Irish and Italian stock This has not been noticeable in my clinic at the Peter Bent Brigham Hospital Boston

Weather — Atrophic arthritis is a disease of temperate zones It rarely affects people in tropical or semitropical countries and I am not aware of any figures as to its incidence in Arctic regions Cold moist climates long have suffered a bad reputation Those who live on the Great Lakes or on the coast are affected in greater numbers than those who are native to the high dry and warm parts of the United States Seasonal variations are noticeable Attacks are commonest in the spring and fall and in a wet spell following a long period of drought The utility of rheumatic joints as weather prophets is accepted by the laity without question but close analysis shows that discomfort comes after

is established scar tissue thickens the walls metaplastic changes result in islands of fibrocartilage or even osteoid tissue and a calcium paste fills the cavity Capsular rheumatism is a term used to identify a periarticular fibrositis involving primarily the joint capsule Tendovaginitis usually is a distinct synovitis of tendon sheaths due to local conditions of pressure and malposition Fibrositis is a clinical concept used to indicate a connective tissue reaction local or general in fascia muscle sheaths and nerve sheaths as the basis of lumbago muscular rheumatism wry neck and pain between joints which clears up without leaving evidence pointing to any other explanation In some cases subcutaneous nodules can be felt which bear a close resemblance to the fibroid nodules of atrophic arthritis

Incidence

Chronic arthritis is one of the commonest of diseases Few individuals if any go through life without having symptoms suggesting rheumatism at some time or other Fortunately the great majority of the attacks are so mild that they receive scant consideration from both patient and physician They are accepted as the ills to which flesh is was and ever shall be heir which doubtless is true Serious instances are frequent enough however to warrant the statement that chronic arthritis leads all other persistent maladies as a cause of economic suffering

A survey in one state (Massachusetts) a few years ago showed that 140 000 persons (3 2 per cent of the population) had arthritis as a major disability In Northern European countries it accounts for 9 to 14 per cent of the cases which are rated as having permanent disability Statistics from the United States suggest that 75 per cent of industrial workers over forty years of age require treatment for some form of arthritis

The relative incidence of the three major types can only be estimated Atrophic arthritis predominates in special clinics because it offers the most serious and constant threat to health In general practice hypertrophic arthritis is much more common and the periarticular forms may possibly outnumber both One s views are colored by the age and occupations of his clientele and by the degree to which the experiences of the special clinics are correlated with those of the general medical and surgical clinics The point is important for if one is led to believe that most rheumatism is of the atrophic type one is likely to permit his diagnosis of particular cases to be colored thereby and a great deal of unnecessary worry and inapplicable treatment can follow

not be compared because of differences in the types of cases selected as well as in technical methods standards and controls Positive results seem most common in young individuals whose arthritis is active and of short duration Negative findings are the rule in older people and those with a long standing indolent process It should be pointed out of course that failure to isolate organisms does not mean that no organisms are or ever were present The chance of recovering them from a small fraction of the blood in circulation at one time or from a bit of tissue or fluid from one joint must be small

Indirect proof has been sought in recent years by utilizing tests for the presence in the body of bacterial toxins and agglutinins and by testing the sensitivity of the skin to bacterial products Evidence is accumulating in many clinics here and abroad that patients with atrophic arthritis have developed antibodies against various strains of hemolytic streptococci in higher concentration and in a greater proportion of cases than individuals in control groups The significance of these results is not well enough understood to permit final conclusions at the present time They certainly are not digested sufficiently to be of value in clinical diagnosis And even these newer methods have yielded negative results in about one-fourth of the cases It is difficult therefore to sustain the contention that atrophic arthritis is a specific disease due to one or a related group of streptococci Other types of streptococci have been isolated in some cases staphylococci and bacilli in others and there is no sharp demarcation of gonorrhea from still others Finally the behavior of the disease is entirely too variable to be explained by differences in the host and non infective factors

Once arthritis is established it may be reactivated by many acute infections This is especially true of the atrophic type but it holds for the periarticular and occasionally for the hypertrophic types as well Disorders of the upper respiratory tract are the commonest offenders The rheumatic individual wisely learns to dread colds and sore throats The more serious the infection the less likely it is to affect the joints perhaps because it forces its victim to go to bed

Foci of Infection —The portal of entry for the infection which ultimately reaches the joints is unknown in the great majority of cases it seems to be the oro naso pharyngeal region Billings was one of the first to suggest that areas which harbor microorganisms might feed them or their toxins into distant regions over a long period of time as foci of infection and that the removal of a focus might cure the disease or stop its progress His suggestion was received with such enthusiasm that a search for a focus of infection is still the first thought that occurs to

or during a storm as often as it does long enough before to be of com mercial value Some unpublished observations are of interest in this regard A few years ago Dr I C Hall and I had several sessions of four hours each with a few assorted arthritic patients in an isolated room at the Harvard School of Public Health in which the atmospheric conditions could be manipulated as desired by Mr C P Yaglou and unknown to us It turned out that when there was a positive charge of electricity in the air all of us felt uncomfortable and the patients thought that their arthralgias were increased but that when the charge was negative we felt distinctly pleasant The humidity and temperature had not been altered Mr Yaglou assured us that the electrical state of the atmos phere is quite as often negative before a storm as after and that it may change with great rapidity

Station in Life — While no class or group of persons are exempt all forms of arthritis seem to be more common and more serious in the de pressed third City dwellers are afflicted with the atrophic type possibly more often than those who live in the country Unsanitary surroundings lack of sunlight and fresh air crowded quarters poorly arranged hours and circumstances of work all have been considered Their common factors seem to be a tendency to lowered resistance to disease and increased opportunities for cross infections

Heredity — Atrophic arthritis is found in the relatives of patients with the disease in about the same frequency as has been noted for rheumatic fever Nearly 20 per cent of my patients gave a history of rheumatoid arthritis or rheumatic fever in their parents brothers or sisters A common way of living working and eating seems a better explanation than to postulate a true hereditary factor

Infection — Bacterial infection is the most important etiological factor without which atrophic arthritis has not been proven to exist This is the most satisfactory interpretation of the tissue changes which have been described of the clinical and laboratory signs such as fever tachycardia lymphadenopathy wasting leucocytosis and increased rate of sedimentation of the red blood corpuscles and of the course of the disease All of these features appear in differing degrees in patients with tuberculous gonorrheal and septic arthritis If the atrophic type consists of the cases of infectious like arthritis that remain after those with known causes are excluded the point at issue nowadays is not whether there is infection but whether the infection is specific

Bacteriological studies of the blood joint tissues synovial fluid and regional lymph glands by many workers have yielded positive results in a variable though usually small percentage of cases Statistics can

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the specialist they are worthless Allergy anaphylaxis and hypersensitivity are such loosely defined terms that their use here only adds confusion to an already complex situation

Trauma is not needed in the full development of atrophic arthritis Many patients however as they enter middle age and improve sufficiently to use their joints in a normal degree show hypertrophic changes which must be accounted for by wear and tear

Endocrine Factors — None of the ductless glands plays a part in originating any type of arthritis This is as true of hyperparathyroidism which alters profoundly the calcium metabolism as it is of pituitary disease which influences the growth of bone Hyperthyroidism rarely is associated with arthritis Cases of myxedema often show an unusual amount of hypertrophic changes on x ray films but an etiological relationship is not clear No disorder of the sex glands has been proved in spite of the difference in the sex incidence already noted Some patients with atrophic arthritis seem to have been endowed with insufficient physical reserves and others with hypertrophic arthritis are full bodied rugged individuals yet there are too many exceptions to conclude that a person s type of construction forecasts the kind of arthritis he will have

Metabolic Disturbances — The arthritis of gout and of ochronosis are the only examples of joint disease due to an error in metabolism Uric acid is handled normally by patients with other forms of arthritis Calcium and phosphorus studies reveal no significant alterations although senile osteomalacia often causes arthralgia due to changes in weight bearing lines The minor variations in sulphur metabolism that have been reported require further confirmation and interpretation The effects of any wasting process can be seen in the occasionally decreased protein content of the blood with a tendency to increase in the globulin fraction Aberrations in the cholesterol content have been found in some cases more often those of the hypertrophic type show elevations and those of the atrophic type lesser amounts No toxin has been found that is not of bacterial origin

It is likewise impossible to assign etiological value to the nutritional disturbances which are so common in arthritis The wasting is part of the disease rather than its cause Fat is taken care of in a normal manner Obesity has no evident effects beyond mechanical stress Protein produces no effects on joints contrary to opinion current at the time arthritis was confused with gout Changes in the absorption of sugar and in blood sugar tolerance curves have been demonstrated but they can be duplicated in normal people and in individuals with other types of chronic disease Patients often have the impression that various articles

most physicians when they see a case of arthritis regardless of type But the search so often is fruitless and the results of extirpation so often are much less than hoped for that many become quite skeptical of the whole theory some have stretched it to questionable lengths Individual reactions to infections vary enormously Frank infections such as quinsy seem to be followed by joint disease in very few Lesser disorders of teeth tonsils and sinuses appear to be as common in patients with hyper trophic and periarticular arthritis as in those with atrophic arthritis or no arthritis at all Nevertheless there are cases in which an infection so mild or small as almost to escape detection appears to be the cause of serious rheumatism It is to be remembered also that more than one infection may be present and that a new one may arise after the joint disease is well established A thorough search for foci is therefore in order in every patient with arthritis What to do about them is a matter requiring wise judgment

Of the various foci it is generally agreed that the *tonsils* are most im portant They were diseased in 30 11 per cent of my cases but had been removed previously in many others Infections about the *teeth* seem to be greatly overrated as a source of arthritis Root abscesses were found in less than 10 per cent of my series It is questionable whether caries or pyorrhea cause systemic effects Too many teeth have been sacrificed simply because these were present *Sinusitis* ranks third 5 per cent in my experience the diagnosis resting not only on cloudiness by x ray or transillumination but also on pus exuding from them In fections of the *prostate gland* apart from gonorrhea are rarely responsible for arthritis The same is true of *pelvic inflammation* in women In fection of the *gall bladder* rarely is linked with arthritis although a few cases have been reported The *colon* and *appendix* often are accused but seldom proved guilty An occasional patient with *ulcerative colitis* has atrophic arthritis and acute arthralgias occur in patients with *dysentery* The bowel is not diseased in *constipation* and evidence of absorption of toxins from a gut which is not the site of inflammation is highly imagina tive

Allergy — Patients with arthritis are no more subject than other people to the well recognized diseases of allergy namely asthma hay fever and urticaria When they occur together the joints may bother more than usual as might be anticipated but the association appears to be purely casual There have been many attempts recently to discern an allergic basis for all atrophic arthritis They may prove helpful ultimately as a means of studying the interaction of bacteria and tissues but as for clarifying the concept of the disease now for the general practitioner and

manual laborer show the greatest changes Symptoms are however entirely unrelated to social or economic status or type of activity The tired business man may suffer more than his gardener The dowager may show larger Heberden's nodes than her dressmaker

Heredity plays no part except as longevity and occupations run in families

Infection plays no direct rôle The general reactions to infection in the body are wanting and the tissue changes do not suggest it It is possible that joints which are the sites of healed infections may be more vulnerable to degenerative influences later on but in most cases there is little proof that this is so Intercurrent infections do not disturb the joints in hypertrophic arthritic patients as much as they do in the atrophic group Areas which serve as foci of infection in the latter are or have been diseased just as often in hypertrophic patients yet attention to them does not impede the development of the arthropathy The symptomatic response to extirpation also is negligible in most cases

Trauma is the most clearly recognized cause of hypertrophic arthritis Experiments show that acutely traumatized hyaline cartilage degenerates and osteoarthritis appears if the joint continues to be used Such a sequence of events is difficult to verify in human beings because it may take many months Baseball fingers are an example They result from multiple small fractures of cartilage and sometimes of bone about the terminal finger joints Microtraumata frequently repeated are responsible most often Damage to joints in sport in work in even the ordinary business of living eventually produces osteoarthritis The joints which are used most such as those which bear weight are the ones to show signs and symptoms first and in greatest degree Postural defects rightly have been emphasized the forward head slouched shoulders sway back tilted pelvis knock knees flat feet All of these insults pile up in the course of time and it is a rare event to prove beyond any doubt that an individual over forty does not have some hypertrophic changes somewhere This type of arthritis is therefore fundamentally due to the ageing process Senescent tissues also are traumatized more easily than young tissues so that the process of joint degeneration is accelerated after middle life Nevertheless the symptoms which are experienced on the basis of these changes usually are due directly to stress and strain and overuse

Circulatory Disturbances — Vasomotor instability is very uncommon and other abnormalities of circulation are not obviously concerned etiologically with the development of hypertrophic arthritis The possibility that they have been overlooked is strong For example osteo-

of foods bother them even to the point of making their rheumatism worse Hypersensitivity has been advanced as the explanation but the matter really appears to be one of fear and distaste for proof of sensitivity is lacking on skin tests and elimination diets I have not seen a case A young college student who had attacks of asthma and pain in the left shoulder showed skin reactions to ragweed and potato a year later he reported that on the few occasions when he had tried potato his shoulder pain had returned He had however no demonstrable arthritis or bursitis

Circulatory Disturbances — Manifestations of vasomotor instability are common in atrophic arthritis They contribute much to discomfort but can hardly be conceived of as influencing the joints directly There is certainly no lack of blood supply in areas that are inflamed In regions long active obliterative endarteritis can be found sometimes

The Hypertrophic Type

Age — Most of the patients have reached middle age by the time that symptoms first appear for the joint changes are in part those of senescence Trauma accounts for most of the cases in young adults The older the patient is at onset the less bothersome the disease is likely to be in either severity or duration In my series of 446 cases 30 per cent began before the age of 40 There were 12 under 20 years old The oldest was 82 The average age at onset was 46

Sex — The benign and asymptomatic forms are found with equal frequency in men and women Traumatic types are commoner in men The menopause marks the onset of or accentuates the disease in women It is curious that Heberden s nodes are seen nine times in women to once in men It is also fair to say that women are symptomatically more aware of degenerative changes in their joints than are men

Race — None is exempt Hypertrophic arthritic changes have been observed in the people of all lands and in the bones of the ancients as well as the moderns

Weather — The disease manifests the most flagrant signs and symptoms among those who dwell in temperate and frigid zones where the tempo of life is fastest and the chances of trauma greatest Hypertrophic arthritic patients are also as apt to be upset by inclement weather as those with the atrophic type but to a lesser degree and for shorter periods of time

Station in Life — Occupation is very important in determining the location and the severity of hypertrophic arthritis The farmer and the

to describe all the pet names that each group of workers has for its particular rheumatic hazards whether intra or extra articular

Circulatory Factors —Arteriosclerotic and senile changes in connective tissue undoubtedly account for much of the muscular stiffness of old age

Relation of Acute and Specific Arthritis to Chronic Arthritis

Rheumatic symptoms may occur in the great majority of acute infectious diseases They disappear promptly and completely in the great majority of cases also and the possibility of residual damage to the tissues of the joints being present and playing a part in the later development of chronic hypertrophic or atrophic arthritis is purely hypothetical Those individuals who subsequently show atrophic changes make the theory attractive In a few cases indeed one sees in retrospect the arthralgia of an acute infectious process as the first attack of arthritis Furthermore the power of infections to affect an already existent joint process adversely is well known There is some basis therefore for giving consideration to such conditions in any discussion of the background of chronic arthritis

The greatest difficulty may be encountered when one tries to distinguish *acute rheumatic fever* from an acute attack of atrophic arthritis Pathologically the Aschoff body is similar to the subcutaneous fibroid nodule but differs in size and in distribution through the body Etiologically the hemolytic streptococci are related to both Clinically their appearance may be identical When one compares large groups of cases minor differences appear in the fever sweats skin lesions and the joints A systolic heart murmur is common in patients with atrophic arthritis but changing heart signs or the development of a diastolic murmur point to rheumatic fever Abnormalities in electrocardiographic tracings are found when the heart is involved and they are helpful because they have not been observed in atrophic arthritis Yet 4 per cent of my 267 cases of atrophic arthritis have valvular heart disease in other clinics the proportion is stated to be as high as 8 and 10 per cent All of the manifestations in the joints are supposed to disappear completely in cases of rheumatic fever but careful inspection shows that minor permanent abnormalities remain in quite a large number They are more apparent as repeated attacks are endured It is also true that very many cases of atrophic arthritis show no residual joint damage after the first attack has cleared up sometimes even after several attacks The response of pain to salicylates is almost as satisfactory in acute atrophic arthritis as

phytic spurs can be produced in the patella of dogs by limitation of their blood supply Injection experiments designed to illuminate the blood supply about human hypertrophic joints have been unsatisfactory The nature of the changes in bone and connective tissue as fibrillation and excessive calcification however are such as to suggest insufficient circulation This is borne out by the relief of symptoms afforded by heat The deficiency may be part of the process of senescence comparable to changes in the skin and in the walls of arteries and veins It has been my experience that people who suffer from their hypertrophic arthritis have more gross cardiovascular disease than others of the same age that is more of them have hypertension arteriosclerosis varicose veins and hypertensive and arteriosclerotic heart disease

The Periarticular Type

Age — Bursitis and fibrositis are found with greatest frequency during the years of greatest physical activity

Sex and *race* play no part except as they influence the more important factor of trauma

Weather — Exposure to wet and cold and draughts is a very common cause of pain described by the laity as a cold in the muscle Transient acute attacks are common in otherwise healthy persons More chronic and recurrent cases are found in older people with hypertrophic arthritis and in miners stokers and others who are exposed most often

Infection — Few cases seem clearly associated with a focus of infection in tonsils sinuses or teeth Possibly the arthralgias of many acute infectious diseases are based on involvement of periarticular structures They are affected also by allergic reactions to diseases sera and drugs

Trauma is the most common cause of periarticular fibrositis Glass arm usually is due to subdeltoid or subacromial bursitis frequently with fibrillation of the capsule of the shoulder and of the supraspinatous tendon baseball players violinists shovellers plasterers and pneumatic drill workers are the chief victims Tennis elbow is a fragmentation of the conjoined tendon of the extensor muscles at the lateral epicondyle of the humerus or a radio humeral bursitis or both it is found in those who play tennis squash or polo and in clothes pressers blacksmiths sweepers violinists and salesmen who carry bags Weaver s bottom is a bursitis of the ischial tuberosity Housemaid s knee is an effusion in the prepatellar bursa Tennis wrist is a tenosynovitis of the extensor tendons at the wrist The list could be extended indefinitely if one were

tuberculous rheumatism is quite unsatisfactory It is rather striking that patients with pulmonary tuberculosis rarely have arthritis

Diagnosis and Treatment of the Atrophic Type

Types of Cases

The disease employs no single pattern of development Some patients are plunged abruptly into a polyarthritis with hot red swollen bitterly painful joints a sustained fever tachycardia swollen glands and spleen Such a storm is apt to subside with reasonable promptitude leaving normal health and few or no scars in the joints Minor variations make these cases hard to distinguish from instances of acute rheumatic fever gout septic or gonorrheal arthritis which in fact some of them are Other patients drag out a miserable existence with symptoms that lead them to be called neurasthenic Their strength insufficient for ordinary demands their asthenic appearance and their easily upset emotional balance outweigh whatever symptoms might be referable to their joints Fever adenopathy and splenomegaly are absent and a cursory glance at the joints shows nothing wrong Months or years later rheumatoid changes are obvious Cases of spinal arthritis not infrequently are so misjudged because the peripheral joints may long be spared Most patients however suffer a destructive arthritis from the beginning which spreads at varying pace to new joints never wholly leaving old ones tachycardia and constitutional signs are prominent but adenopathy splenomegaly are not Local redness and heat in the joints are not common and pain is less than stiffness and weakness

Nor are the patterns fixed A case of the acute type may have several such attacks at intervals of months or years or may change at any time to the chronic progressive type The chronic type may suffer an acute exacerbation which speeds its downhill course The neurasthenic type may become acute or progressive An arrested case may be re activated in malignant fashion and a hopeless case may find its fight suddenly won These uncertainties when considered with the fact that causes for them are often not to be found make forecasts perilous

Precipitating Factors in Atrophic Arthritis

Study of the patient s immediate past often reveals circumstances which seem to have contributed to his arthritis In cases of sudden onset there may have been an attack of tonsillitis quinsy influenza or

in rheumatic fever and as in acute gout in young people One may have to wait years for the development of typical signs in the heart or joint to make the correct diagnosis The majority of patients with rheumatic fever are ten years younger than those with arthritis It may be that the cardiovascular apparatus is more vulnerable in youth and articular structures more in adults the etiologic agents being much the same

Gonorrhea causes arthritis in a small proportion of cases 3 to 5 per cent but the cases are numerous because the disease is common It begins within a few weeks or months of the primary infection It upsets many joints at first and then shows a curious tendency to clear up in all save one usually a knee The majority of cases heal completely and promptly A few progress into chronic atrophic arthritis and still fewer prove to be frankly infectious Bursæ tendon sheaths and other periarticular tissues are involved more widely than in rheumatic fever and atrophic arthritis Diagnosis is important because fairly specific treatment is available and the prognosis is so favorable One should insist however upon demonstration of the organisms or a history of recent gonorrhea Cases of arthritis due to gonorrhea years ago are not often proven The complement fixation test is helpful only in excluding it if negative Falsely positive tests are too frequent in atrophic arthritis to warrant reliance on them alone and harm can be done the patient with too vigorous heat therapy in such cases

Scarlet fever causes an acute arthritis resembling rheumatic fever in about 10 per cent of cases *Typhoid fever* occasionally involves the spine in a severe arthritis which may clear entirely after months or may progress to fusion of several vertebræ *Bacillary dysentery* frequently causes a polyarthritis which tends to heal About half of the cases of *undulant fever* suffer an atrophic type of rheumatism which vacillates with the fever may be accompanied by joint effusions and yet leaves no clinical signs when the disease is spent The basis of the aches and pains in and between joints which are such essential features of *influenza grippe* and *upper respiratory infections* is not clear They seldom prove to originate arthritis but may aggravate it

Tuberculosis and *syphilis* of the joints have been described elsewhere They need to be mentioned here only because of the mechanical stress and strains which they may cause in uninvolved joints thus leading to hypertrophic and periarticular forms of arthritis This is also true of septic joints which have stiffened in awkward positions and of anterior poliomyelitis when muscular atrophy results in faulty balance The theory has been advanced recently that the tubercle bacillus may cause arthritis without actual invasion of the joint tissues but proof of such

appeared but they are not as important originally as they are in hypertrophic arthritis

The following list shows the frequency with which the various joints were involved in my series of 267 cases of atrophic arthritis

Fingers (interphalangeal and metacarpophalangeal joints) 70 per cent

Knees	54 per cent	Dorsal spine	26 "
Ankles	5? " "	Hips	26 " "
Wrists	48 " "	Sacroiliacs	20 " "
Cervical spine	40 " "	Toes	14 " "
Lumbar spine	35 " "	Jaws	4 " "
Elbows	34 " "	Sternoclavicular	0 5 " "
Shoulders	34 " "		

I have not seen a case of arthritis of the ossicles of the ear or of the cricoarytenoid joints although it is possible that they exist With these exceptions it is apparent that the disease can and often does extend throughout the body This list differs from others only in the assertion of the commonness of spinal arthritis All agree that the wrists and ankles rarely are attacked in the hypertrophic type and the specific finger joints only scarcely less so

In the active stage of atrophic arthritis the affected joints are *swollen* with exudate which distends the synovial space and the bursæ and infiltrates the soft tissues in the immediate neighborhood The appearance of the fingers is described as fusiform because the swelling often is as symmetrical as a soldered connection between pipes Elsewhere as in the knee and wrist the distension of bursæ and tendon sheaths may give rise to smooth prominences on top of the spindle shaped mass As activity abates and the fluid is absorbed the outline of the joint shrinks toward normal depending on whether the synovial effusion or the bursal or tendon effusions last longest Palpation reveals the resilient or doughy feel that would be anticipated Motion of the joint causes no feeling of crepitation or as in long standing effusions and tenosynovitis a rub as of brake bands tightening The swelling may last a few days or may remain for weeks or months and is diagnostic of active disease Care must be taken to distinguish it from apparent swelling due to atrophy of interarticular tissues which lingers after healing has begun It is also wise to differentiate periarticular from intra articular swelling for the former probably represents a less active stage and permits more vigorous use Joint swelling is difficult to detect in shoulders and hips but the leathery rub in chronic cases shows its presence The only physical sign of swelling in the spine is an occasional soft crepitus in the neck that the patient hears more often than the examiner feels

some other manifestation of infection in the upper respiratory tract a month or two before the joint pain begins In cases of stealthy appear ance there may be a prodromal period when the appetite fades the body weight decreases a sense of unusual fatigue and lack of ambition hampers ordinary pursuits and perspiration and chilliness suggest vasomotor disturbances A change in dietary habits is noted occasionally such as follows the adoption of a fad or a weight reducing remedy or a struggle to get along without teeth or with new ones A long siege of caring for sick relatives the shock of death or business reverses a change to work under trying conditions may usher rheumatism in One patient who finally died of inanition after years of complete invalidism claimed that his joints first swelled within a few days of the disclosure of his wife s infidelity Yet it is striking that no background of infection or debility can be found in many patients the arthritic storm appears in a clear sky

Symptoms and Signs in Joints of Atrophic Arthritis

A general survey of the patient s joints reveals several items of value in distinguishing atrophic arthritis from other types of chronic arthropathy In the first place, it is invariably a *polyarthritis* Occasionally one joint may be affected so much more than others that at first glance the case appears to be a monarthritis but close inspection always shows alterations in other joints Instances of true *monarthritis* are limited to rare cases of tuberculosis tertiary syphilis and direct infection and injury and these can be detected without great trouble It is a good plan to list all the joints that are diseased when one first studies the patient as a means of measuring the subsequent course A more important point is the ten dency for atrophic arthritis to attack the small peripheral joints first and most severely The proximal interphalangeal joints often are in the lead followed quickly by knuckles ankles knees wrists and elbows It is remarkable that the terminal interphalangeal joints of the fingers are seldom involved in sharp contrast to the hypertrophic type A third point is the symmetrical distribution of the joint lesions After the patient has had a few attacks over several years one should be surprised not to find both knees involved or both ankles or both wrists or elbows All the fingers and knuckles then may show disease but similar joints may show the same degree of alteration the third knuckle on each hand or the fourth proximal interphalangeal joint for example Fourthly the joints are selected by the disease without regard to weight bearing use or trauma These factors emphasize and speed the changes once they have

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movement This state of constant misery seriously taxes the patients serenity Some of them become bitter spitefully inviting their long suffering relatives to share their troubles just for one day Few are able to live it down as successfully as a surgeon who has carried a heavy load of teaching and operating effectively and happily despite the fact *that he has not known a single day s freedom from pain in twenty years* It is stated often that arthritic patients complain out of all proportion to physical cause the inference being that a simple emotional reorientation is all that is necessary to gain comfort There is no denying that some of them become hypersensitive and impatient and that new philosophies and therapeutic fads lift them temporarily out of themselves But in stances of assumed pain are rare The distress has adequate basis in the disease if the signs are searched out if its prolonged course is remembered and if care is not taken to keep the use of the joints within the range of their safety Granting again that there is no correlation between the amount of pain and the severity or activity of the disease that some with *mild cases have a great deal and others with advanced* changes have none nevertheless pain remains a very useful guide for the control of each patient If all of them lived within the boundaries at which pain began there would be few cases of serious deformity

There are three main varieties of pain There is the steady non fluctuating ache directly in the joints heightened by use disappearing after rest A throbbing quality is added when the areas are red and distended Then there is the pain of spasmodically contracted fibrosed atrophied muscles seen later in the disease Neuritic pain is common early and late If peripheral nerve sheaths share in the fibrositis or if they are stretched or pressed upon by the swollen joints paresthesias *are noted distally* Numbness *burning stinging chilling are common in* the arms when the shoulders are diseased Involvement of the cervical and dorsal spine may cause pressure on or inflammation of the dorsal root ganglia resulting in radiculitis This explains the pain referred about the head eyes jaws chest and abdomen in such cases Some mimic pleurisy and angina pectoris closely but tenderness can be dem onstrated between the ribs and rest in extension gives relief Arthritis of the hips and lumbar spine may give rise to pain in the knee

When a patient with atrophic arthritis says that his pain is worse in the morning after a night s rest and wears off as the day s activities are begun it is due to swelling about the joint It is a sign that the joint has been used *too much Further use may grind down the effusion to a* point where motion is painless but this trauma does harm When rest is allowed the swelling returns the next day it is as bad and the disease

The *functions of the joint* are limited at first due to pain swelling, muscle spasm and atrophy and general malaise. The degree of restriction is a useful measure of the activity of the disease only when effusion is present. In joints which are the site of repeated or long continued activity irregular articular surfaces due to villi pannus and eroded cartilage limit function still more. In terminal stages when untreated or unsuccessfully treated ankylosis causes permanent immobility. It is necessary to determine which of these factors causes the dysfunction as a guide to prognosis and the prescription of exercises.

The *deformities* which may result also come from several causes. Flexion often is due to pain. Muscle atrophy and contractures pull in an unbalanced fashion causing lateral or antero posterior dislocations. Injudicious use adds its quota. Weight bearing is an important source of flattened ankles and distorted knees. The deformity is permanent if bony ankylosis bridges the gap that once was joint. Often however what feels like ankylosis and even looks like it in roentgenograms is a rigidity due to fibrous contraction of the capsule and periarticular structures. A long trial of proper exercises is warranted before the joint is given up for lost; the small success that can be expected is well worth the effort. Occasionally the disease burns out leaving relaxed hypermobile joints. In such a case the cartilage is likely to be well preserved, the malady having centered on muscles and connective tissue. It is my impression that these patients always were double jointed, a quality easily accentuated by a mild persistent inflammation of periarticular structures.

It is worth repeating that tendon sheaths bursae and connective tissue in general are involved regularly in atrophic arthritis. The degree may be small in the average case which progresses slowly. In acute cases particularly in gonorrheal arthritis it may outrank the disease in synovia and cartilage. Its identification is important because one may find that what appears to be a serious exacerbation of the arthritis is only a mild recurrence of fibrositis or bursitis.

Pain in the acute stage of atrophic arthritis is distinctly less than it is in acute rheumatic fever or gout, although a rare case can tolerate neither heat nor the weight of bed coverings. In certain cases affecting the spine pain is an overwhelming experience because it is so steady and enduring. Patients with the average indolent chronic process tend to have only moderate pain which leaves them fairly promptly every time their joints are put at rest. An aching soreness in the general region of the affected parts is common for months after signs of activity seem to have departed. The patient winces when the shins are touched; the heels and wrists long may be sensitive and there is fear of shaking hands or any sudden

may grow excessively In late relatively inactive cases the general skin surface may be thin dry and pebbly or greasy Areas of erythema and purpura may be found from time to time particularly on arms and legs Pigmentation may be a striking feature in severe cases vitiligo in others Psoriasis occurs in a few When it affects the nails the terminal phalangeal joints show rheumatoid changes Obliterative endarteritis and sclerodema may be seen in the terminal stages of malignant cases

Subcutaneous fibroid nodules can be detected in about 10 per cent of cases As with tophi in gout their frequency varies directly with the powers of observation of the physician They are found most commonly on the extensor surface of the wrist and elbow less often over the sacrum patella scapula scalp and fingers They are hard round bodies two to four millimeters in diameter which can be moved freely apart from skin and bone but may be attached to tendon sheaths A few reach a larger size if pressure stimulates their growth I have seen them the size of half a walnut shell on the olecranon process Tenderness is rare They may persist for months or years much longer than in rheumatic fever Similar nodules are seen in fibrositis and sometimes in the sacroiliac region in individuals without joint complaints but in atrophic arthritis I have found them only in serious cases

Edema of the feet and lower legs appears at times when the joints of the knees and feet are greatly swollen It is increased when the limbs are dependent It is not of cardiac or renal origin

Constitutional Signs and Symptoms of Atrophic Arthritis

The patient with atrophic arthritis displays elsewhere in his body the effects that one would expect of a chronic infection They vary according to the stage of the disease its activity and the individual s economic and psychologic ability to cope with it

Fever is present in the acute phases It is rather less than it is in rheumatic fever unless the case be one of gonococcal or other frank infection but ranges between 100 F and 102° F for several days or weeks The *pulse* is accelerated to 90 to 110 beats to the minute The *body weight* suffers moderately five to twenty pounds being lost *Lymph nodes* are palpable in the neck axillae and groins in the majority of cases The enlargement is not great and they are not often tender The *spleen* is barely palpable in one-eighth of the cases most of them young people

It is in the *chronic stage* that the real work of devastation is accomplished for acute attacks last but a short time and are found in only a certain fraction of all cases Here the temperature may never be found

gets worse Every effort must be made to teach him the fallacy of "limbering up" an inflamed area If however he says that his pain is gone on rising and reaches its peak by evening it is due to fatigue No harm has been done and a little rest or less vigorous activity will take care of it Pain that wakes him out of a sound sleep at night is due to a release of muscle spasm which permits motion in the joints which it had guarded

Stiffness is a symptom that keeps pace with pain but may linger long after discomfort has gone Patients distinguish it quite clearly from the immobility of ankylosis They mean by it an interference with joint function that is considerable at times particularly after rest and yet can be made less by use or still more rest Stiffness often is the natural result of swelling in and about the joints Late in the disease when these are absorbed it is due to spastic atrophied muscles or to shrunken capsules

Atrophy of muscles probably occurs in all cases except the mildest and most transient Weakness as a general complaint is well explained by inactivity pain and malaise The shrinkage of the muscles which control actively diseased joints goes beyond this It is seen in the interossei and palms when the fingers are spindled in the forearm when the wrist is swollen in the thigh when the knee is involved and so on Fibrillary tremors may accompany it The atrophy may appear within a few days of the onset of joint pain Sometimes it outranks all the other joint signs and is the chief cause of disability In severe cases the wasting may be extreme the poorly covered bones seeming to magnify the enlargement of the joints Some degree of it often is permanent the normal muscle mass never being fully restored In the average chronic case however its progress fortunately is slow and much of it can be prevented by appropriate rest and exercise

The *tendon reflexes* tend to be hyperactive about the affected joints They are absent only when ankylosis prevents reaction They are normal in the healthy joints

Atrophy of the skin is extremely common It may not be very evident in febrile cases but is quite prominent in the hands of the chronic cases On the dorsum it resembles thin parchment On the palms it is dead white cold sometimes exhibiting a marbled cyanosis at others a reddening of the thenar and hypothenar eminences *Sweating* may be so profuse that the hands drip moisture Over distended joints such a shoulders and knees the skin may have a pale or pink shine Marked redness is not seen nor the ruddy cyanosis fringed by distended veins as in gout The hair may disappear from affected parts in a rare case it

Fatigue is present in most cases It may be the chief complaint The patient customarily is very tired in the morning finds life bearable by noon and is his usual self by evening Much of it is the natural result of a persistent process that causes malnutrition Even in the healed moderately advanced cases performance is less than normal The joint deformities may be such as to make movements difficult Action requires more concentration and effort than it does in well persons A teacher of piano who had been very ambitious returned to her work after two years of atrophic arthritis and found that she could keep in balance if she worked six hours and rested sixteen when she increased the one or decreased the other fatigue set in quickly followed by arthralgias

Fear is responsible for much fatigue fear of painful days and nights fear of invalidism worries over the cost of the disease and its effect on the family economy the struggle with burdens of housework and children that cannot be laid aside Then there is the frantic drive to keep in motion because stiffness follows rest and freer motion temporarily follows use Few arthritic patients become truly neurasthenic although tempers are sharpened and courage runs low Neurasthenia does not cause inflammatory joint disease It is unwise to discount complaints because they seem to be out of reason or to erase fatigue by stimulation to further activity

Disorders of the *cardiovascular system* are not common Acute cases in young people are subject to confusion with rheumatic fever as has been mentioned A few of them have pericarditis Valvular heart disease occurred in 4 per cent of my cases elsewhere its incidence has been reported as high as 8 to 10 per cent Systolic murmurs are heard very frequently during periods of tachycardia without evidence of organic change Hypertensive and arteriosclerotic heart disease was found in only 5 per cent of my series which is much less than it is in hypertrophic arthritis Varicose veins seldom are bothersome Vasomotor disturbances are common and may be quite annoying

The *lungs* are not involved Patients with pulmonary tuberculosis rarely have atrophic arthritis *Pleurisy* seems to be part of the process in about 1 per cent of cases of acute polyarthritis *Pneumonia* sometimes increases but as often allays the joint disease

Iritis is a rare complication It is found generally in young patients particularly those who have gonorrheal arthritis

Concomitant disease elsewhere in the body usually is absent Three fourths of my patients with atrophic arthritis suffered from arthritis alone

above normal or it may not go above 99 6° F In a few patients this slight fever is present daily for many months Tachycardia at a rate of 90 to 110 is quite general persistent and a fair measure of activity Lymphadenopathy and splenomegaly are not so common The general nutrition may suffer markedly Much of it is due to atrophy of muscle and bone some to chronic disability and its effect upon appetite Ten to fifty per cent of the original *body weight* may be lost over a period of a few months Some patients are reduced to living skeletons In my series of cases whose average age was 38 8 years and whose arthritic age was 6 8 years 28 per cent were more than twenty pounds under weight 41 per cent were normal and 30 per cent were over weight 32 pounds average

Whatever the weight careful study of the patients habits often reveals much to criticize *Diet* analyses on my cases showed that only 37 per cent were taking normal diets A considerable excess of carbohydrates was admitted by 47 per cent chiefly in the form of candy sugar and pastry The *vitamin intake* appeared to be deficient in 50 per cent These figures are not sufficiently different from those collected from control groups of patients and well people to warrant a suggestion that malnutrition is a cause of arthritis but their therapeutic inference is very much worthwhile Chronic invalids often are plied with extra food the feeling being as formerly in tuberculosis that mere gain in weight is a sign of improvement The more the appetite for regular meals fades the more they are urged to take nourishing snacks between times and so the less they eat at meals Milk generally is avoided Fruits are excluded because of acidity or expense Green vegetables are not apt to be chosen by bedridden people Meat is sometimes feared for its supposed relation to gout Correction of these mistaken habits and ideas does much to improve the general nutrition

Indigestion is common Specific diseases of the liver stomach and bowel are no more frequent than in people without arthritis Sagging viscera and dilated colons appear in so many individuals with and without disease that they have not been proven to be liabilities The usual complaints of gas distention belching anorexia nausea abdominal discomfort and irregular bowel movements which these arthritic patients mention are explained adequately by their faulty habits of eating chronic disease and particularly by the misuse of cathartics laxatives enemata and irrigations How frequent they are needs no comment I can recall one poor patient who was taking on medical advice magnesia epsom salts mineral oil and enemas every day topped off by belladonna paregoric and the hot water bottle!

When tuberculosis is a possibility skin tests and roentgenologic studies should be made first and the chances weighed of creating a sinus tract from a cold abscess Routine study of the synovial fluid should include an enumeration of the different types of cells and a search for bacteria by smear and culture Other tests can be added as particular circumstances warrant The red blood cells range from a few hundred to a few *thousand to the cubic millimeter in the synovial fluid of atrophic arthritis* Grossly bloody fluid or an icteric index over 5 5 point to mechanical injury The leucocytes in the synovial fluid of atrophic arthritis number from 50 to 5 000 of which less than half are neutrophilic granulocytes Larger numbers and a higher percentage of neutrophils indicate frank sepsis Cultures usually are sterile unless the white cell count is greatly increased The complement fixation test is positive in gonorrheal arthritis and the Wassermann test is positive in syphilitic arthritis Sugar is slightly decreased from the normal of 80 to 110 milligrams per cent in atrophic arthritis values below 60 are found in septic joints A hydrogen ion concentration close to 7 0 suggests infection for the normal is 7 35

X rays in *Atrophic Arthritis*

Decrease in the density of the shadows cast by the portions of bones adjacent to the joints affected by atrophic arthritis suggests decalcification This often is the first sign to be revealed by a roentgenographic film Some degree may persist for years in spite of a diet rich in calcium and a fair return of function Disuse causes further thinning and its temporary extension throughout the shaft The details of bony structure are preserved although small circular areas within which nothing is seen may appear adjacent to cartilage Such punched out areas are found also *in gout and in hypertrophic arthritis A smooth faint clearly out* lined shadow marks the presence of fluid in bursae and periarticular soft tissues Early the bone ends appear to be their normal distance from each other Loss of cartilage is shown by a narrowing of this space It may come quickly in the more infectious cases or may require months or years As the bones approach each other their surfaces tend to show irregularities but eburnation is absent or very slight Ankylosis seems to be present when the joint space is obliterated and bony trabeculae can be traced from one bone to the next Much of this is artefact caused by *the film being taken with portions of the bones overlapping so that* true complete fixation can be accepted only with clinical confirmation Small deposits of calcium sometimes are visible in cartilage and in tendon attachments

Laboratory Data in Atrophic Arthritis

Anemia is not a feature of acute polyarthritis except for an occasional case resembling rheumatic fever In chronic cases a moderate hypochromic anemia is rather frequent Twenty five per cent of my cases had hemoglobin values between 50 and 70 per cent and red blood cells ranging from 3 5 to 4 2 million to the cubic millimeter Increases in the *white blood cell* count are confined to the acute stages the average being 9 000 to 13 000 to the cubic millimeter rarely above 18 000 Careful examination of the stained blood smear in any degree of activity however shows a slight excess of neutrophilic granulocytes often with two lobed or banded nuclei denoting immaturity Leucopenia with a relative lymphocytosis is seen in some severe cases The *sedimentation rate* of the red blood cells is more rapid than normal in all cases If no other reason exists this points to activity of the arthritic process and the speed proves to be a fair measure of its severity It is normal in remissions Since it is also normal in hypertrophic arthritis it can serve sometimes in differentiating the two It is however but little more sensitive as an indicator than the heart rate

The *chemical constituents of the blood* are found in normal concentration There is no alteration in the amount of sugar and sugar tolerance tests show normal utilization The calcium and phosphorus values are unaltered In states of malnutrition the protein may be decreased moderately particularly the albumin fraction

Blood cultures taken in the usual manner are sterile

The *urine* shows a small amount of protein occasionally during febrile periods more rarely a few red blood cells and hyaline casts In the great majority of cases they are absent and renal function tests are normal

The *gastric contents* and *feces* reveal nothing of interest

The *basal metabolism* is within normal limits in the absence of fever Young arthritic patients sometimes present certain suggestions of hyperthyroidism but the coexistence of the two diseases is unusual It is more common for older patients with a long standing arthritis to have a moderately low rate

A sample of *synovial fluid* should be secured promptly in every case of acute febrile polyarthritis with effusion It can be withdrawn easily under aseptic precautions if a large joint such as the knee is affected and it may reveal information of diagnostic value Delay may lead to serious joint destruction if sepsis is present and the need for drainage is not realized Tapping is unnecessary in chronic cases without fever

beyond in both directions Pain often is referred down the arm rather than confined to the joints *Flexion is better preserved than rotation* and extension and it is the position assumed when ankylosis occurs being fostered by chair arms and bed pillows Fibrous contraction is much more common than bony fusion It can be detected by feeling *the tense biceps tendon when extension is attempted*

The *shoulders* rarely show obvious enlargement There is tenderness on pressure over the head of the humerus also over the bursae if they are affected Pain on motion may be severe Neuritic pain down to the *elbows or fingers is very common at rest in a dependent position* There is atrophy of all the shoulder girdle muscles Motion is limited in all directions particularly in abduction Fixation occurs in adduction flexion and inward rotation Ankylosis involving the humerus is rare *but it is seen between the acromion process and the clavicle*

Of the *toes* only the first phalanx usually is involved It may proceed to bony union with little clinical appreciation of the fact The metatarsophalangeal joints often are affected Soreness is greater than active pain Flexion deformities cause great trouble in walking and in wearing shoes The *ankles* show changes similar to the wrists irregular doughy swelling suggesting synovial effusion or a general puffiness Gravity *adds an element of edema shown by pitting of the skin on pressure* Pain is variable Tenderness along the tibiae is very common Atrophy of the lower leg is obvious Motion is greatly limited As the ligaments give way the tarsal bones are forced down destroying the long arch of *the foot Fusion occurs in the position of eversion and plantar flexion* Much of the stiffness is not permanent A useful foot remains as long as some inversion and extension are preserved

The *knees* are affected in the majority of the older patients and those with very persistent arthritis Both are affected although one may excel the other temporarily Swelling may be extreme The patella floats away from the femur this can be demonstrated by ballottement if the periarticular *tissues are held firmly Bony enlargement is simulated because* of the wasting of the thigh muscles The quadriceps femoris is atrophied the earliest and most permanent disability is that of extension The hamstrings often are contracted The patella may become fixed to the femur The tibia seems to be displaced posteriorly at times but this must be confirmed by x ray films A soft sticky crepitus is palpable even audible on motion especially when listened for with the stethoscope *Pain may be severe Tenderness is located at the joint margins* particularly on the medial side and in the popliteal space Ankylosis is not uncommon in partial flexion and posterior and lateral subluxation

Roentgenographic study is unnecessary in the diagnosis of arthritis It cannot differentiate clearly between septic arthritis rheumatic fever gonorrheal arthritis and atrophic arthritis Tuberculosis of the joints may look much like it at times Mild hypertrophic changes in thin elderly people may cause confusion and so do mechanical injuries and gout Infection may be superimposed upon these Nevertheless the roentgenologist can be of the greatest service to the physician if he is given the clinical history and findings particularly in planning orthopedic measures or operations Films are desirable also at intervals as a record of the progress of a case It is well to request films of normal joints for purposes of comparison with the diseased joint in question

Special Features of Individual Joints in Atrophic Arthritis

The Fingers — The terminal joints are not often grossly swollen except with psoriasis of the nails Minor changes can be seen on x ray films as frequently as in the other finger joints Ankylosis in an hyperextended position occurs if the case be severe and untreated The middle row of phalangeal joints is the characteristic point of attack for atrophic arthritis Only a few may suffer in the first and early bouts but as time goes on the rest are included Their fusiform appearance has been described Motion is greatly limited in flexion and extension first by pain later by fibrosis and contracted tendons finally by ankylosis A few of the metacarpophalangeal joints invariably are affected along with the fingers Swelling often is not great Pain and disability are apt to be more pronounced Lateral deflection is common Usually it is due to the position assumed in inactivity but occasionally it is so strongly maintained as to suggest muscle spasm in unequally atrophied muscles Subluxation may be found When ankylosis occurs in flexion and ulnar deviation the hand may be quite useless The thumb commonly is involved Atrophy of the interossei and the thenar and hypothenar eminences is prominent

The *wrists* may show a smooth fusiform swelling extending over the hand and half way up the arm When of lesser degree the contours are more irregular the puffiness being mostly on the dorsum and the ulnar side Pain is not as active as in other joints but an aching soreness may be complained of for a long time Motion is limited in all directions particularly in extension and in chronic cases is accompanied by a sticky rub The use of the fingers is restricted The grip is weak Atrophy of the forearm can be extreme Ankylosis tends to take place in flexion

The *elbows* may show little swelling or a diffuse enlargement well

are in current use to emphasize certain striking features as Strumpell Marie arthritis, spondylose rhizomelique, spondylitis ankylopoietica, etc.

Fortunately it is not common, 6 per cent of my series of 267 cases. Contrary to ordinary atrophic arthritis, males are more often the victims than *females, 10 to 6.* Young adults are almost exclusively attacked; my cases were 24 years old on the average, though an occasional case may begin in childhood or as late as 38. The specific etiology is indeterminate; *gonorrhea rarely is found.* *The onset is insidious or acute* and the background is that which has been described already. Pathologically and by x-ray films the bodies of the vertebræ are more or less decalcified. If the process starts *before growth is complete* the bodies may remain small and there is an overgrowth of the spinous processes. There is very little diminution in the spaces between the vertebræ and no concave bone edges. Calcium is deposited at the outer margins of the intervertebral discs and particularly in the anterior and lateral ligaments. A thin straight line joins several or many vertebræ as seen in lateral roentgenograms. It is unlike the curved lines of interlocking osteophytes in the hypertrophic type and the whole appearance of such a rigid spine is that of a bamboo pole. Changes typical of atrophic arthritis take place in the facet joints and the costovertebral joints. The sacroiliac joint fuses early in the course of the disease in almost all cases. The hip and shoulders are affected in about one quarter of the patients. Otherwise the peripheral joints strangely are spared. Only one third of my cases showed arthritic changes in the arms and legs after years of trouble and in a few they were hypertrophic, quite independent of the original process.

Pain *in the back is the outstanding symptom.* It may be so severe as to suggest a neoplasm of the spinal cord or vertebræ. It may not abate for months or years until fusion is complete. It is relieved by rest *in a recumbent position, although for a few hours it is made worse.* When activity is over a milder pain may persist due to mechanical stresses. A few patients complain very little; their trouble may not be discovered *until years later.* *The pain of radiculitis is quite common.* *When it is* present without pain in the back the true diagnosis may not be suspected. Sharp lancinating pain about the head, ribs, abdomen and down *the legs bring other possibilities to mind.* *Malnutrition often is severe.* Fatigue and nervous instability are at times overwhelming.

The pathognomonic signs are rigidity of all or of a portion of the *spine and immobility of the chest.* *The ribs may expand only an inch* or less on inspiration. Breathing is all abdominal. When the lumbar area is involved the normal curve is lost. In the dorsal region there

The *hips* commonly are involved in a minor degree Extreme changes are met with in tuberculosis sepsis and in the rarer forms of spinal arthritis Local pain may be quite severe or absent It can be referred in the sciatic radiation Sometimes the only sign of hip disease is pain in the knee There is wasting of the glutei Muscle spasm holds the leg in flexion adduction and internal rotation Ankylosis is fairly rare

The *sacroiliac joints* are involved seldom in ordinary cases of atrophic arthritis They are injured so frequently by postural and mechanical trauma and by minor infections probably that bony ankylosis is said to be a normal finding in x ray films of patients of middle age Swelling is not detected Pain and disability may be extreme but temporary

The *temporo mandibular joint* frequently is painful Slight swelling may be detected The difficulty in opening the mouth at times makes feeding a serious problem Fortunately ankylosis rarely is permanent

The *sternoclavicular joint* is diseased occasionally The gonococcus is not responsible for most cases as sometimes is said to be the case The disability is not great

The Spine — Pain in the back is a very common complaint of patients with atrophic arthritis who are of middle age The neck has a painful crepitant rub on motion It is stiff in the morning The posterior muscles of the neck are tender The dorsal and lumbar portions are involved less often but they seem to be the origin of the radiating pain about the ribs abdomen and down the legs that these patients suffer Physical signs are absent aside from tenderness on pressure near the spinous processes No swelling or muscle atrophy can be seen No permanent residue is left as in the peripheral joints Roentgenograms show nothing abnormal or just a little atrophy of the vertebral bodies and a narrowing of the spaces between them or the degenerative changes that are consistent with the age of the patient It is to be remembered that there is nc synovia between the vertebræ hence no possibility of effusion and anky losis The costovertebral joints may show narrowing and rarefaction o bone The facet joints are difficult to visualize It is difficult to de termine in many patients whether the symptoms arise from synovitis o these small joints or from an inflammatory reaction in the abundan connective tissue or from hypertrophic spondylitis

There is a malignant form of atrophic arthritis of the spine whicl was described independently by several workers about fifty years ago Pierre Marie von Strumpell and von Bechterew believed that thei cases represented different entities At present they all appear to b different stages or degrees of the same process Since the resemblanc to atrophic arthritis is close no special name seems necessary but a fev

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may be a marked kyphosis without sharp angulation If fixation occurs in this position a distressing situation results The patient is unable to lie in bed without the legs elevated Sometimes rest is secured only by lying in a hammock or forward on a bed table Walking is an effort because the eyes scarcely can be raised off the ground Fortunately the first two cervical vertebrae usually are spared so that some slight motion of the head remains The fixed distorted thoracic cage favors the development of emphysema and cardiac disease Occasionally the rigid spine is perfectly straight and the patient walks with a stiff military attitude Bending is impossible Objects are picked from the floor by flexing the knees and reaching with the arms

The buttocks and erector spinal muscles are atrophied The knee jerks are hyperactive Fever may be absent or slight and prolonged The laboratory findings are similar to those for ordinary atrophic arthritis

Atrophic Arthritis in Children and the Aged

The disease is very rare in young children When it occurs usually there is a marked generalized reaction with wasting palpable lymph glands spleen and liver and a rather marked anemia with lymphocytes The terminal finger joints may be affected The pathological tissue changes are similar to those seen in adults Amyloid degeneration of various organs may be seen The course of the disease is the same as it is for atrophic arthritis and indeed there seems to be no reason for distinguishing it as a separate entity or Still s disease after the name of the man who first described it in 1897 although this often is done There is as little reason for isolating the occasional adult case with lymphadenopathy splenomegaly skin pigmentation and anemia under the heading of Felty s syndrome Original attacks of atrophic arthritis are quite uncommon in elderly people Careful examination sometimes shows typical changes in the joints pointing to a previous attack The cases that I have seen have appeared in conjunction with other serious disease carcinoma of the prostate and lung in two cases and after an operation for carcinoma of the sigmoid colon in one

Differential Diagnosis of Atrophic Arthritis

The identification of typical well established cases of atrophic arthritis presents no difficulties The chief points are the history of several attacks of polyarthritis with some degree of relief in the intervals and the physical signs in peripheral joints of swelling subnormal function and de

formities and atrophy of muscles and skin It is very important to distinguish the cases from hypertrophic arthritis for the outlook and the therapeutic necessities are quite different This will be discussed under *hypertrophic arthritis* *The spinal form should be thought of in emaciated* young adults with pain of a radiating character

The similarity of *rheumatic fever* to atrophic arthritis has been mentioned Major distinctions are electrocardiographic changes and later the signs of valvular heart disease in rheumatic fever Minor points of difference are the more severe arthralgias in rheumatic fever their more prompt and permanent subsidence under salicylate therapy a higher fever lesser lymphadenopathy and muscle atrophy The fingers are not typically fusiform in rheumatic fever and the changes in the joints disappear more completely Bacteriological agglutination tests are not as yet of proved value in distinguishing them

Infectious arthritis is a septic form of atrophic arthritis to be distinguished by more abrupt and severe general symptoms and more rapid disintegration of a few joints It is wise to obtain synovial fluid early in suspected cases A leucocyte count of 5 000 or more and the detection of organisms by smear and culture point to the need for prompt surgical attention

Gonorrheal arthritis may simulate atrophic arthritis very closely before it settles down in one or a few joints It clears more promptly and leaves little residue It also tends to localize in mild cases primarily in periarticular tissues Most cases occur in close relationship to acute gonorrhea of the genital tract but a few probably follow reactivation of an old focus such as the prostate Identification of the specific organism in material from genital lesions or from affected joints should be demanded for a positive diagnosis The gonococcus complement fixation test is positive in proved cases It is quite unreliable by itself for it is not infrequently positive in exacerbations of atrophic arthritis with fever when there is no history or bacteriological evidence of gonorrhea These false positive reactions are negative later on particularly when the temperature is normal

Acute *gout* leaves the affected joints entirely normal after a few days of severe pain and swelling Such attacks are repeated over a period of many years before chronic gouty arthritis appears The vigorous health of the patient and the absence of atrophy of muscles and skin make this look more like the hypertrophic than the atrophic type The acute symptoms subside promptly under colchicine and the uric acid content of the blood usually is more than normal Tophi are found in two thirds of the chronic cases

Tuberculous arthritis may be considered in cases arising in children It is however usually limited to one or a few joints In them the doughy fluctuation and the muscle atrophy are striking especially because of the absence of local signs of inflammation Roentgenograms are very suggestive for they show definite disorder in the end of the bones without any loss of cartilage In difficult cases it is necessary to secure fluid or tissue from a joint for microscopic study and inoculation into a guinea pig

Syphilitic arthritis rarely causes confusion Other signs of syphilis are present The serological tests are positive The arthritis of secondary syphilis clears promptly with or without treatment The neuropathic joint of Charcot in the tertiary stage is revealed by the painless destructive non ankylosing monarthritis and the positive serology

Prognosis of Atrophic Arthritis

The mild cases that recover fully without any treatment to speak of must be set aside That they are numerous is evident when one recalls the minor abnormalities in the joints of many patients with valvular heart disease and the frequency of pain in the joints in many acute infectious diseases Though they are pathologically and clinically similar to atrophic arthritis at the time they lack the progressive character of the chronic cases It would be very helpful to know why they do Until that time comes we must estimate the prognosis on the basis of the chronic cases with clear evidence of well established disease in the joints It is impossible to speak of any of these as being cured permanently Dramatic recoveries are rare The usual course is one of increasingly frequent relapses interrupted by less frequent and less complete remissions over a period of years The most careful forecasts are based on the observations of many patients in special clinics which labor under the handicap of dealing almost exclusively with the worst cases and with very limited hospital facilities for the care of prolonged illness Such forecasts arrive at these average results one fourth of the patients recover one half of them improve and one quarter become worse Of my 267 clinic cases seen over a ten year period one third did not return This can be taken as the measure of the patient s willingness to accept treatment or of the clinic s educational effectiveness Of those that were treated for half a year or more 40 per cent had good results 29 per cent had fair improvement and 30 per cent were unimproved or worse It is gratifying that those who were cared for the longest showed distinctly better results than those who were seen only a short time

Much of the outcome depends upon the attitude of the physician He should be the family medical advisor if cases are to be seen and treated early enough to prevent deformities and arrest the progress of the disease where a good level of physical activity can be retained Failure is certain if he centers his attention on a quick cure or relief He must plan and execute *a program which considers all the disabilities in the patient* and his environment over a period of years He should be cheerful if only to encourage the patient The experience of those who have spent much time with these unfortunate individuals is that such cheerfulness is warranted for analysis of the reasons for failure shows how much more might be done if a few conditions were corrected such as more hospital beds for chronic disease and more physiotherapy The physician must be honest also if he is to retain the confidence of the patient who is *persuaded easily to try this and that magic cure only to be disillusioned* And he must take infinite pains to explain the patient s disease to him in order to secure intelligent cooperation

Much also depends upon the attitude of the patient If he has the will to get well he is likely to succeed If he cannot accept his problem if he loses courage and gives up he is apt to become a high grade cripple His social situation may be a great handicap Poverty interferes seriously with rest in a hospital or at home There are few institutions in this country where arthritic invalids can get adequate care for a sufficient period of time without a great deal of money Riches on the other hand do not insure success as often as not they lure the patient to experiment with absurd short cuts to health Family strife and grief weigh heavily on a cripple whose nerves already are frayed by pain

The outlook for life is good Death rarely can be attributed directly to atrophic arthritis As Garrod said The disease has little tendency to shorten life although it is apt to deprive the patient of much that *lends value to life*

It is hazardous to forecast the future in a disease which has no definite end which undergoes surprising remissions and which is stimulated to renewed activity by so many factors In general it would appear that the older the patient is at its onset the milder it is in symptoms and course Yet with good treatment children may do as well as adults The earlier treatment is instituted the more is the likelihood of preventing serious crippling this is particularly true of atrophic arthritis of the spine *Acute febrile attacks carry a good immediate prognosis slowly progressive* afebrile cases must be taken with great concern Pain is of no value as a guide patients who suffer tortures may regain a high degree of health and function while others comfortably progress to a severe

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to limit the concessions very narrowly and that he knows that this inferior plan will take more time in the end and will allow more destruction of joints to take place

In securing local rest for the joints splints of various sorts often are very helpful They relieve pain and relax spastic muscles They aid in preventing or overcoming contractures and they hasten the absorption of edema and effusion With heat they permit early resumption of active use of the joints Instances are a cock up plaster cast or splint for the wrist or foot and a bivalved plaster for the knee They are worn at night and for much of the day particularly after exercises Comfort also is increased by a cradle which keeps the bed covers off the legs or by a pillow beneath the covers at the end of the bed which prevents pressure on the extended feet When the patient is more ambulatory elastic bandages and adhesive tape can be used to continue local rest and support

There is a fine art in getting the patient out of bed He should be allowed to be up for only a few minutes one day next a few minutes twice a day then a gradual increase in the number and duration of the periods is ventured according to whether or not morning stiffness follows Weeks or months may pass before an ordinary day is gained and still longer before less than twelve hours in bed at night can be tolerated Privileges are curtailed sharply by every relapse or by a threat of relapse with a cold or grippe or an exhausting experience Lest these views be considered too radical let it be stated that many mild and early cases do not take such an unbearable time and that for the others it is the only program that can warrant optimism The problem of these patients is essentially that of adjusting their activities to the limits set by chronic disease Overstepping is followed surely by progression and fatigue Health and comfort are possible within those limits

Hospital bed rest is greatly to be preferred to rest at home for only in a hospital is essential physiotherapy available There too are freedom from household responsibilities and protection from too long or too many visits from friends and the cheering discipline of a regular schedule If these are not being obtained then much of the benefit of hospitalization will be lost Fresh air and sunlight are very helpful for afebrile patients Sleeping out of doors is an excellent tonic for the chronic asthenic invalid provided that he is warm In these respects the old pavilion type of hospital excels the modern skyscrapers Bed baths are necessary for patients with fever and for those whose pain or disability makes a tub hazardous If the patient must be treated at home as is far too often the case the physician should make every effort to estab-

invalidism Stiffness after rest is an excellent indicator of active disease in and around joints Unfavorable signs are malnutrition persistent tachycardia anemia and leucopenia marked muscle atrophy and sub cutaneous fibroid nodules

Treatment of Atrophic Arthritis

In the treatment of atrophic arthritis emphasis is to be divided equally between the patient and the joints The physician cannot assume that if he takes care of the individual the joints will take care of themselves nor can the orthopedic surgeon succeed by concentrating on the joints exclusively Cooperation is essential but the physician s is the greater responsibility He is the one who is most likely to discover the disease he is best able to acquaint himself with the many pertinent details in the general situation and to him the family looks for the administration of treatment The cooperation of the patient is even more essential He needs instruction as to the nature of his affliction in suitable doses He should be told that arthritis is like tuberculosis diabetes mellitus and peptic ulcer in that eradication is not possible but that much can be done to prevent suffering and crippling There is no hope of cure by any single measure He must plan a campaign with due regard for its severity and persistence and the economic circumstances of his family His chief reliance is on those complementary opposites rest and exercise

Rest in bed obviously is necessary throughout the acute phase of any arthritis It should last as long as constitutional and local signs are present and the temperature and pulse rate are elevated This usually takes four to eight weeks A more sensitive indicator of activity is the sedimentation rate of the red blood cells It remains rapid for some time after fever has subsided and if its warning is heeded there will be fewer recurrences Continuous bed rest is just as necessary for patients with chronically active processes in their joints in order to control malnu trition and to relieve the mechanical strains of weight bearing This may require a month more often several months or even a year or so in severe cases such as those of atrophic arthritis of the spine Activity of the process must be assumed so long as pain or stiffness are present after rest for they indicate swollen articular tissues This is a very strenuous program It is accepted with greatest reluctance from a short sighted view of the disease or an underestimation of future possibilities Never theless experience proves that it is wise and that any compromise has its dangers Where it is impossible to carry out this ideal schedule as in most clinic patients it is all the more essential that the patient be urged

Diet — A normal diet is necessary for every patient with arthritis Great care should be taken to see that it is optimal in all respects We are all wont to assume that what we choose instinctively to eat is right without considering the part played by fads fears and customs Eccentricities of diet are common to chronic invalids and often add to their handicap of malnutrition They must be cleared away by education A pint of milk every day is the surest way of providing a proper supply of calcium it is not fattening or constipating Extra fruit may be advisable for patients with anemia bony tenderness and a tendency to bruise easily A sample normal diet follows

Breakfast	Orange juice or tomato juice	1 large glass
	Cereal (farina or whole wheat or oatmeal)	1 serving
	Egg — any style	1
	Toast	1 slice
	Milk	1 glass
	Butter	as desired
	Cream ½ cup heavy or ½ cup light	
	Coffee tea kaffee hag sanka or postum	
Luncheon	Soup clear or cream	as desired
	Egg or fish or cold meat	1 serving
	Salad — fresh fruit or vegetable	
	Green vegetable	
	Milk	1 glass
	Bread butter	1 slice
	Dessert of fresh fruit nuts or ice	
Dinner	Soup	as desired
	Meat (lean) or fish or poultry	1 serving
	Green vegetables	
	Other vegetables	
	Milk	1 glass
	Bread butter	1 slice
	Postum or kaffee hag or sanka	as desired
	Dessert of fruit plain pudding jello or plain ice cream	

General directions Eat 3 meals a day regularly with no food between meals Drink plenty of water

Meat Red meat liver sweetbreads oysters salmon white fish poultry game Pork (except bacon) sausage and fat fish are not to be taken frequently

Green vegetables Asparagus string beans brussels sprouts cabbage lettuce spinach celery tomatoes beet greens broccoli cauliflower okra Canned or frozen vegetables are almost as effective as fresh

Other vegetables Potatoes corn squash beans turnips beets carrots cucumber egg plant parsnips

Dairy products In addition to milk and cream cheese of any sort particularly cottage cheese and buttermilk are desirable

Fruits Berries bananas melons dates raisins figs apricots peaches pears apples nut These may be taken in any quantity Canned and dried fruits are permitted

lish thorough supervision enlisting therefor the aid of a responsible relative and a nurse be she graduate practical or community health

The bed should be a hospital cot for the convenience of the attendants It should have firm springs with hinges to permit raising the head and knee sections The patient is instructed to change his position frequently often assuming that in which the joints are in physiological position This is accomplished by removing all pillows from under the head and placing a small one underneath the shoulders thus straightening the neck and raising the ribs The arms are abducted the elbows and knees straight High grade invalids need assistance in moving about A Bradford frame may be helpful if bed sores appear

Exercise is necessary from the very beginning in all patients with arthritis It supports the appetite and the will to fight It aids the absorption of exudates from articular tissues and it combats atrophy of muscles and fibrous tissue contraction Some motion however slight should be encouraged in even the most sensitive joints yet great care should be exercised to avoid whatever exhausts or causes an increase in pain It is not advisable to put each affected joint through its full normal range of motion once a day as has been advocated by many workers Such passive motion may be painful to a degree that requires anesthesia The forcible breaking and stretching of inflammatory tissues increase the injury and may cause disaster I have seen a wrist broken by unintelligent physiotherapy and a cervical vertebra fractured allegedly by an osteopathic treatment The only safe motion is that which the patient himself will perform Each joint in succession is guided and supported by the physician or a trained attendant in a manner that reduces fear and extends the motion slowly and steadily When pain is experienced the patient relaxes and then repeats the exercise several times This is done once or twice every day increasing the time and the energy expended so long as pain and stiffness are not greater on the following morning Weight bearing is deferred until the joint is painless and its muscles strong enough to give support

General exercises also are beneficial They may be limited at first to such as promote deep breathing or stretching As improvement progresses they can be made more vigorous in all the healthy joints Contraction of the glutei and the abdominal muscles helps to erase the backache due to a long maintained lumbar curve The knee is protected by tightening the quadriceps femoris The feet are strengthened by flexion and extension The discipline of such daily activity is essential to prevent rest from degenerating into a state of inanition or pettish dissatisfaction

Diet — A normal diet is necessary for every patient with arthritis. Great care should be taken to see that it is optimal in all respects. We are all wont to assume that what we choose so instinctively to eat is right without considering the part played by fads, fears and customs. Eccentricities of diet are common to chronic invalids and often add to their handicap of malnutrition. They must be cleared away by education. A pint of milk every day is the surest way of providing a proper supply of calcium; it is not fattening or constipating. Extra fruit may be advisable for patients with anemia, bony tenderness and a tendency to bruise easily. *A sample normal diet follows:*

Breakfast	Orange juice or tomato juice	1 large glass
	Cereal (farina or whole wheat or oatmeal)	1 serving
	Egg — any style	1
	Toast	1 slice
	Milk	1 glass
	Butter	as desired
	Cream ¼ cup heavy or ½ cup light	
	Coffee, tea, kaffee hag, sanka or postum	
Luncheon	Soup, clear or cream	as desired
	Eggs or fish or cold meat	1 serving
	Salad — fresh fruit or vegetable	
	Green vegetable	
	Milk	1 glass
	Bread, butter	1 slice
	Dessert of fresh fruit, nuts, or ice	
Dinner	Soup	as desired
	Meat (lean) or fish or poultry	1 serving
	Green vegetables	
	Other vegetables	
	Milk	1 glass
	Bread, butter	1 slice
	Postum or kaffee hag or sanka	as desired
	Dessert of fruit, plain pudding, jelly or plain ice cream	

General directions: Eat 3 meals a day regularly with no food between meals. Drink plenty of water.

Meat: Red meat, liver, sweetbreads, oysters, salmon, white fish, poultry, game. Pork (except bacon), sausage and fat fish are not to be taken frequently.

Green vegetables: Asparagus, string beans, brussels sprouts, cabbage, lettuce, spinach, celery, tomatoes, beet greens, broccoli, cauliflower, okra. Canned or frozen vegetables are almost as effective as fresh.

Other vegetables: Potatoes, corn, squash, beans, turnips, beets, carrots, cucumber, eggplant, parsnips.

Dairy products: In addition to milk and cream, cheese of any sort, particularly cottage cheese, and buttermilk are desirable.

Fruits: Berries, bananas, melons, dates, raisins, figs, apricots, peaches, pears, apples, nuts. These may be taken in any quantity. Canned and dried fruits are permitted.

Avoid concentrated starches and sugars such as macaroni spaghetti pie cake and candy These may be indulged in occasionally but should not be a part of the daily menu

This diet can be varied to suit particular needs Febrile patients do better with a light diet which omits some vegetables and fruits and contains more fluids fruit juices and milk Patients who are under weight need more calories These can be supplied best in carbohydrates and there is no convincing evidence that arthritis interferes with their metabolism Meals should be eaten at regular hours to promote appetite and good bowel function Frequent feedings are not helpful in gaining weight indeed they may prevent it A good method of reducing is to eat little and often

It is often desirable to add vitamin preparations Vitamin B is serviceable for anorexia and digestive unrest Cod liver oil is rightly accorded general approval one or more tablespoonsful daily may have an astonishing effect on the spirits and attitude of an asthenic arthritic patient The concentrates of vitamins A and D which are so commonly used as substitutes of the natural oil or in patients of normal or excess weight seem to have little demonstrable result The good reports of huge doses of vitamin D as used recently by some workers appear to be based upon uncritical enthusiasm No theoretical consideration points to a need for them and there should be at least evidence of their safety before they can be recommended

Defecation receives far too much attention from chronic invalids An assumption of masterful indifference is better If the proper kind of food and amount of fluids are taken it is of little concern whether the evacuations are of any particular size or regularity The daily resort to laxatives and cathartics of all kinds is largely responsible for the bowel irritability that so often is attributed to toxins or stasis Plain liquid petrolatum occasionally is indicated Enemata of a pint of plain water every other day provide relief from scybalous masses in the rectum Colon irrigations have no particular advantage and their too frequent use may promote a spastic mucous colitis Acidophilus milk still has a few advocates but it does nothing that a balanced diet cannot do as well

Infection —The search for infection should be thorough in every case Its treatment depends upon a careful consideration of the participation of the infection in the arthritic process its effect upon general health the duration of the arthritis and the patient s age Diseased tonsils should be removed with little hesitation if the patient is young i e under 30 If he is older a very definite history of tonsillitis and frequent sore throats and clear physical signs such as inflammation of the anterior faucial pillars and palpable tender cervical glands are neces

sary to warrant removal The wisdom of the operation in any one over fifty is questionable The optimal time for removal is a matter of dispute My belief is that delay is unnecessary except for a few weeks after an acute tonsillitis The status of the arthritis is not a deterrent unless it be so acute as to occupy all attention There may be an increase in joint activity for a short time which is unfortunate but this can be handled with better end results than if one temporizes with an ineffective program of building up resistance first The patient should be warned not to hope for too much from tonsillectomy Dramatic results are rare and usually transient particularly if the rest of the therapeutic program is neglected The benefits are to be found in possibly fewer attacks of diseases of the upper respiratory tract better general health and a joint process that is more amenable than before

Extraction of teeth is a major operation in sick individuals It is to be advised on the *opinion of a good dentist that infection is present* and in such stages as the patient can tolerate Teeth are *not* to be sacrificed because they are devitalized or because they exist in the mouth of an arthritic Every effort should be made to preserve serviceable teeth by attention to cavities and pyorrhea and to replace others with *proper dentures A mouth that is wholly or partially edentulous* is an important factor in an inefficient digestive apparatus

Infection of the paranasal sinuses is to be dealt with according to the advice of a conservative specialist Other foci are treated also as independent disorders along accepted lines not with hope of direct *alleviation of the arthritis* but *for the purpose of improving the general* health

Vaccine Therapy — The use of vaccines in the treatment of atrophic arthritis may be compared fairly to their status in the common cold Many physicians do not use them at all a few are convinced of their value *They encourage the patient and they afford the physician a good* opportunity to establish strict control over a long time by a visit every week They have no effect if other treatment is not carried out meticulously The younger the patient the shorter the course of his arthritis and the more it resembles infection the more likely are beneficial results *to follow Older patients with well established damage to joints are* poor candidates Of the many preparations on the market those made from various strains of hemolytic streptococci are best They are injected under the skin or into a vein the latter has been advocated as the better way but it requires more care The series of injections of *increasing amounts is planned at five to seven day intervals for four to six months* If any one is followed by a flare up of manifestations in the

joints the next dose is the same or less for such reactions are undesirable

Foreign Protein Therapy — In patients who are young whose general health is good and whose arthritis is recent and accompanied by fever a few injections of sterile foreign protein may be distinctly worthwhile There often follows a prompt subsidence of fever and of symptoms in the joints which lasts a few days or weeks or rarely months or years The results in the great majority of cases of long duration and definite derangement of the joints and of the general nutrition are too poor to warrant a trial Many preparations have been tested among which are milk peptone proteose casein Malaria has been induced with unsatisfactory effects Standard typhoid vaccine appears to be the best a small amount 20 million organisms is injected intravenously and then larger doses at three day intervals the size being sufficient to cause a febrile reaction This purpose is the opposite of specific vaccine treatment Whatever benefit may appear will do so after six to eight doses more are merely upsetting to the patient

Physical Therapy — Heat is an indispensable aid in the treatment of arthritis It increases the local circulation of blood and lymph promotes the absorption of fluid from joint tissues reduces pain and spasm and is a general tonic No particular method of furnishing heat excels The simplest and cheapest is as good as the most elaborate Wet heat is afforded by cloths soaked in a hot saturated solution of magnesium sulphate or by flaxseed poultices Hot baths are given with difficulty to painful cripples and may exhaust them Alternating hot and cold baths require more hardihood than the arthritic invalid can be expected to have Dry heat is much easier to use in the form of hot salt or sand bags a hot water bottle a simple lamp or electric baker or electric light cradle These are used occasionally for comfort or according to a regular schedule in association with massage

It is now possible to raise the temperature of the body to any desired level and keep it there by various new electrical apparatus *Diathermy* causes heat to penetrate deeply but there is no evidence that this is more beneficial than external heat Its results are disappointing often quite unpleasant It is not recommended *Radiothermy* has been supplanted by *air conditioned* cabinets and simple hot boxes Each has been tried on different kinds of patients with varying degrees duration and repetition of exposure The results show that they have some value in acute arthritis in young healthy individuals Such cases are a very small minority For all the rest the treatment is too upsetting and exhausting It requires constant and expert nursing care and an intake

of fluid and salt sufficient to make up for the loss in perspiration Perspiration in itself is of no value for no toxic substances have been demonstrated in it

Massage is excellent if given gently and skillfully by a qualified physiotherapist three to seven times a week A vigorous and homespun variety may be harmful Its services are greatest in the chronic indolent cases but it can be used with due caution in acute stages also

Pool baths also are excellent in the reeducation of atrophied muscles without the strain of weight bearing Unfortunately they are available to very few

Roentgenotherapy has been used extensively in Scandinavian clinics on all types of arthritis It has received little attention in the United States Its best effects are said to be found in cases of bursitis and tendovaginitis It does nothing to joints with effusion or destroyed cartilage or chronic synovitis *This reduces its availability in atrophic arthritis to* those few cases with major and recent involvement of periarticular tissues

Endocrine Therapy — Thyroid substance is of value to the individual with the signs and symptoms of myxedema and a low basal metabolic rate The few patients with atrophic arthritis who meet these requirements are in middle age and their joint disease is old and quite inactive When given to patients with acute arthritis thyroid increases their discomfort Estrogenic substance theelin or progynon in large doses is of value in women who are passing through the menopause with difficulty It relieves nervous tension and vasomotor instability The effect on the arthritis is indirect

Drugs — None is known to possess a specific effect on the pathological process in the joints Pain is controlled without medication in chronic cases that are receiving adequate local and general rest The usefulness *of pain as a guide to treatment has been stressed When an analgesic* is desired a salicylate is the best One or two tablets (0 3 gm gr v) of acetylsalicylic acid (aspirin) several times daily usually are sufficient More are needed for severe acute cases Then it seems better to use sodium salicylate 1 0 gm (gr xv) combined perhaps with an equal amount of sodium bicarbonate four to six times a day This is necessary for only a few days or a week or so Pain that does not submit promptly suggests *the use of measures already discussed such as splints heat and foreign* protein injections Pain that still persists should suggest a search for other cause septic joint malignant disease of bones cord tumor etc Morphine is not indicated Oil of wintergreen often feels grateful on hot swollen joints Amidopyrin (pyramidon) should never be used because of its possible inhibiting effect on the production of granulocytes nor

joints the next dose is the same or less for such reactions are undesirable

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flourish on the gambling spirit of people who are glad to try their luck on escaping the difficult program that nature eventually enforces

It has been observed that jaundice sometimes is accompanied by a remission of arthritis which lasts for a few weeks or months Since no safe method of producing jaundice exists it can hardly rank as a form of therapy Injection of bile and of bile salts have been without results In the few cases that I have seen the disease of the liver was debilitating enough to compel bed rest for many weeks which was adequate to explain the improvement in the joints

Climatotherapy — Fortunately a good climate is only a pleasant luxury in the treatment of arthritis Most patients recover in their native atmosphere if they have the determination and the proper care It is wise to encourage them to do so because a trip to some salubrious resort is beyond the means of most of them If the patient is to derive any lasting benefit the visit should consume at least six months preferably a year or more When he returns he is likely to find new family stresses added to the old ones to which he must become adjusted The physician in planning the therapy for a period of years must consider whether the small extra gain of the pilgrimage is worth its cost in the sacrifices which it exacts from the other members of the household There are many spas in Europe and the United States which unquestionably do excellent work When one tries to analyze the reason for their success it is hard to be impressed greatly with the healing qualities of their various waters or their mud or their high sunshine quotient but one frankly admires their skillful psychotherapeusis their vacation atmosphere their good hotels and their physiotherapy Their danger lies in attributing magical properties to ordinary phenomena This leads by easy stages to uncritical acceptance of fads from freak diets to foot twisting What really is needed is a greater number of beds available for chronic illness in general hospitals throughout the country or in institutions affiliated with them so that the staffs of each may participate in sound developments in medicine

Psychotherapy plays an important rôle in the care of the arthritic invalid It is applied adequately and unconsciously by the physician who demonstrates his competence to deal with every situation as it arises his patience with an enduring foe and his understanding of seemingly illogical and unwarranted complaints Very fe arthritics require the services of a psychiatrist When they do they should not fall into the hands of one who believes the disease to be of psychological derivation

Correction of deformities is the duty of the orthopedic surgeon It would be lightened materially if every case were treated vigorously as

cinchophen (atophan) which is unpredictably hepatotoxic Neither of these drugs possesses any advantage over salicylate and the wary physician knows that they are concealed in many proprietary mixtures

Sedatives may be used to aid sleep during an acute exacerbation They are unnecessary after a few days They are indeed deleterious because they often leave a sense of depression in the morning and encourage overdoing in the day Continuous unconsciousness is not essential rest is compatible with wakefulness For nervous tension an afternoon nap works better than a drug to produce sleep at night If pain interferes acetylsalicylic acid is indicated

For anemia ferrous sulphate 0 25 gm (gr iv) or reduced iron 0 6 gm (gr x) three or four times a day are useful In a disease such as arthritis where malnutrition of any degree has a deterrent effect on the patient and his joints it seems wise to accept minor deficiencies (80 per cent hemoglobin and 4 000 000 R B C per cu mm) as clinically significant The maintenance of optimal values is worthwhile Transfusions have been advocated by many for resistant cases One or two large (500 c c) transfusions are preferable to frequently repeated small ones A potent liver extract parenterally is simpler and sometimes is effective

Sulfanilamide has been used too recently to judge its status clearly It has been a disappointment in rheumatic fever In a few cases of chronic arthritis it has added to the anemia and leucopenia and has not aided the joints

Arsenic as Fowler s solution has an ancient reputation for tonic and hematopoietic properties that does not seem deserved Iodides likewise have tradition as the only evidence of their value Sulphur in any form is useless in arthritis No reasonable basis for it is apparent and clinical trials by men of experience have been failures Gold salts (myocrysin and solganol B oleosum) seem to produce beneficial effects occasionally but they cause far too many toxic reactions on skin and kidney to permit them to be advocated for general consumption Ortho iodoxybenzoic acid marketed as amyodoxyl and oxoate causes transient and variable improvement Given by mouth it produces nausea and epigastric burning when introduced intravenously it causes fever and often thrombosis and sloughing at the site of injection It is not recommended

It is fruitless to review further the amazingly long list of antirheumatic remedies Some show ingenuity as bee venom histamine and choline iontophoresis and chaulmoogra oil Others are thoughtlessly conceived as pills of concentrated spinach Many are improper combinations of sedatives salicylates laxatives and potentially harmful drugs They

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Correction of deformities is the duty of the orthopedic surgeon. It would be lightened materially if every case were treated vigorously as

described Much can be done for the arthritic derelict by simple corrective braces splints and casts Manipulative or surgical measures may be indicated such as synovectomy arthoplasty and reconstruction operations Washing out a chronic effusion is helpful at times Sympathetic ganglionectomy and rami ectomy have been without effect on joint disease

To summarize success in the treatment of atrophic arthritis depends on

1 Early and accurate diagnosis
2 Adequate rest for the patient and his joints
3 Supervised exercises particularly guided active motion
4 The correction of activating factors such as infection mechanical stresses malnutrition
5 A program which includes permanent supervision of health and the early detection and care of relapses

Diagnosis and Treatment of the Hypertrophic Type

The onset of degenerative changes in joints is as stealthy as other manifestations of the ageing process in the hair and skin The onset of symptoms is also hard to date It is difficult to believe that anyone is forever unconscious of the distress which they cause yet only a minority seek medical advice for its alleviation Trauma is a precipitating agent in many instances but the joint changes usually are so well established when the patient is first studied that one must seek for other and earlier factors to explain the whole picture Ill health is not one of them in fact the patients are likely to resent any suggestion that they are unfit to do their full share of work Their situation is unlike that of the patient with atrophic arthritis who can recall his first attacks fairly distinctly and who offers a variety of predisposing factors

Signs and Symptoms in the Joints of Hypertrophic Arthritis

Careful physical examination shows hypertrophic changes of varying degrees in many joints although symptomatically only a few are active at one time The disease is much more apt to be clinically monarticular than the atrophic type The joints which are affected are those which are used most whether to bear weight or to do work They are the knees and the spine particularly in the cervical and lumbosacral areas and those of the right extremities in right handed individuals In contrast to atrophic arthritis symmetry is not a feature and the wrists

elbows and ankles are attacked very rarely My 466 cases of hypertrophic arthritis reported symptoms in the knees in 60 per cent the fingers in 52 per cent lumbar spine in 50 per cent cervical spine in 45 per cent shoulders in 43 per cent dorsal spine in 30 per cent hips in 30 per cent sacroiliac joints in 30 per cent feet (static) in 15 per cent and the temporomandibular joints in 0 5 per cent

The appearance of a hypertrophic joint gives little indication of its symptomatic state *Tenderness often is so slight that a fair amount of pressure must be exerted directly on the articular margins to elicit it* Commonly the joint itself is insensitive and the patient winces only when the surrounding area of muscular and tendon insertions is squeezed The overlying skin shows no redness or heat Whatever enlargement is present is hard knobby *smoothly irregular A fusiform shape is not* seen because there is no thickening or edema of the periarticular tissues Synovial effusion is of infrequent occurrence and short duration and it outlines the joint or its associated bursæ Motion discloses crepitus which feels like the crunching of dry snow It can be heard by the stethoscope and a star patient may assert that her rusty squeaks announce her descent of the stairs to people in distant parts of the house The knee is the most spectacular performer A shoulder rub is so universal in persons over forty as to be without significance Pain and tenderness however seem to have little effect in themselves on the mobility of the joint *Whatever restriction is found is due to the interlocking of osteo*phytes or the irregularity of the abraded cartilage or temporary muscular spasm Motion is never lost completely save in the sacroiliac and a few other joints of the spine

The pain bears no relation to the degree of arthritis that is visible *to the naked eye or on x ray films The bony spurs on the vertebræ* are greatly in excess of symptoms No distress at all is so common that some writers have used the term arthrosis to imply that such cases are different from clinically active ones Other patients for the most part young adults have much more pain than they have physical signs The *reason is that spurs cartilage and bone are devoid of nerves* but these are plentiful in the periarticular soft tissues which are pinched or stretched *by the deformed joint and which show the effects of wear and tear before* the harder tissues do The quality of the pain which is experienced is *variable It has been noted already that tenderness frequently is absent* It is never very great *A sense of discomfort is commoner* than one of pain or there is a steady ache which does not interfere particularly with use Severe arthralgias always are due to traumatic or mechanical causes Paresthesias and referred pain often are outstanding Their

source in arthritic areas is likely to be overlooked because they wander far from the joints of origin and appear near other joints or organs A superficial numb burning stinging sensation or lancinating pain should lead to a search for arthritis Stiffness is experienced more generally than any other symptom Characteristically pain and stiffness appear on use of the hypertrophic joints and abate with rest In contrast to atrophic arthritis they reach their maximum toward the end of the day and their minimum in the morning perhaps after a short limbering up' period

There is no atrophy of the skin in hypertrophic arthritis Whatever skin changes are found can be explained on the basis of work and senescence a dry thick callused epidermis or a thin wrinkled parchment with pigmented keratoses Vasomotor instability is not encountered Excessive perspiration is absent Subcutaneous fibroid nodules are found rarely except possibly in cases complicated by fibrositis They are to be felt also at times over the sacroiliac joints regardless of symptoms

Atrophy of muscles often is absent When it is found it is rarely disabling in degree It appears to be strictly proportional to the amount of disuse or to senile wasting and it can be improved fairly promptly by exercises Spasticity is uncommon Stiffness that is persistent in spite of rest appears to be on the basis of fibrositis and changes due to age

Constitutional Signs and Symptoms of Hypertrophic Arthritis

Patients with active hypertrophic arthritis are healthy people to all appearances Nothing about them suggests invalidism or infection Their temperature is normal They have no tachycardia or no enlargement of the lymph glands liver or spleen that are not attributable to other causes than the joint disease Their teeth are innocent or show nothing more than an ordinary state of disrepair No infection is present in the tonsils or sinuses Diseases of the upper respiratory tract often make aching hypertrophic joints feel much better rather than worse for they enforce rest

Laboratory studies confirm the impression that nothing is wrong Hypertrophic arthritis in itself does not alter the numbers types or appearances of the blood cells the erythrocyte sedimentation rate the chemical composition of the blood the urine feces or sweat

Roentgenographic films of hypertrophic joints which are more than slight in degree or duration show clearly recognized abnormalities There is narrowing of the joint space from loss of cartilage The outline of the

cavity of the joint may be irregular but it is not obliterated for fusion does not occur except in the sacroiliac joints and between osteophytes Osteophytes occur on the margins of joints as rounded or hooked over growths The details of bony structure are normal save for an occasional case that shows the cystic areas of lessened density in subchondral portions which are found also in the atrophic type and in gout Decalcification is not a feature Eburnated surfaces stand out sharply and deposits of calcium may be seen also at tendon insertions or in bursæ

Types of Cases

In spite of the fact that they conduct themselves as if they were well significant disease can be found elsewhere in the bodies of patients with hypertrophic arthritis in the majority of cases Eighty per cent of my series had such disease as compared to 70 per cent of the atrophic type Some allowance can be made for the difference in the average age of the patients Experience shows however that many of these maladies aid in the production of arthralgias It is essential to delve deeply into the patient s past history and social arrangements and to perform a thorough physical examination This results in the discovery of at least one factor *in every case for which treatment is beneficial directly or indirectly to the* joints al o The situation in hypertrophic arthritis therefore is more *manageable than it is in atrophic arthritis where the most painstaking* efforts may reveal no definite infection Since the factors are many it *is convenient to think of them as forming groups of cases of hypertrophic* patients which of course overlap in many ways

The Traumatic Type — *Misuse and overuse of joints are the principal* reason why hypertrophic arthritis causes distress Seventy five per cent of my 466 cases showed evidence of mechanical stresses and strains *Postural errors* are the commonest source of discomfort

When the *longitudinal arch of the foot is pronated* the astragalus sinks down between the calcaneus and the navicular bones This stretches the muscles and ligaments beneath and forces the metatarsals into eversion It results from disease in the ankle or from arthritis of the hip which causes external rotation or simply from the habit of toeing outward It causes pain in the foot and tenderness along the tibia and on the medial superior aspect of the knee which is invariably knocked Experiment will show how difficult it is to walk splay footed without buckling the knees Diagnosis of flat foot is made not by noting a flat footprint for many arches are normally low or lax but by observing the position of the foot

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Roentgenographic films of hypertrophic joints which are more than slight in degree or duration show clearly recognized abnormalities There is narrowing of the joint space from loss of cartilage The outline of the

strain on the sacroiliac joint Finally when none of the above causes for tilted pelvis are present it is wise to look for inequality in the length of the legs

Occupational hazards are numerous In time they lead to much hypertrophic arthritis in farmers laborers machinists and others Accidents and injuries in sport in traffic and at work frequently produce acute traumatic arthritis which may be followed much later by chronic joint disability The sequence of events is fairly clear in cases of hemarthrosis altered alignment due to fracture into the joint or badly united fractures or abnormal joint mobility due to torn or stretched ligaments such as occurs when the shoulder has been dislocated several times or when the knee or ankle have been sprained repeatedly In too many cases however the original injury is not so well-established and the interval between it and the arthritis is so long that the relationship is questionable Legal proof for purposes of compensation then is hard to obtain Such proof should include in addition to evidence of injury to the joint affected knowledge as to the previous condition of that joint The testimony of x ray films is more impressive than a record of physical findings but it is rarely to be had There should be no more than a reasonable time between the symptoms due to the injury and the onset of symptoms of arthritis Compensation may thereupon be allowed to the time when the joint is restored to the condition in which it was known to be before the injury

Other causes of traumatic types of hypertrophic arthritis are to be found in diseases of the bones Distortion of an epiphysis by infection may lead to considerable irregularity in the contour of a joint A slipped epiphysis or a minor grade of failure of the head of the femur to form a stable ball and socket joint with the acetabulum can result in malum coxæ senilis Osteitis deformans may distort weight bearing joints uncomfortably Partial disintegration of a joint by atrophic or frankly septic arthritis promotes hypertrophic repair when use is restored *Poor muscular control alone may cause strain* Atrophy of a portion of the erector spinæ by anterior poliomyelitis for example may produce scoliosis Hypertrophic changes in the hands sometimes is due to constant pressure on crutches or a cane

The Fatigue Type — Fatigue is as common in hypertrophic as in atrophic arthritis It was a feature in 72 per cent of my cases and in 7 per cent it was the chief cause of disability It has an adequate basis contrary to what seems to be the situation in the atrophic type but often it must be searched for diligently because of the patient s failure to recognize it or admit its effects It is not physical fatigue

on walking and at rest and by finding appropriate symptoms of strain Feet which have been pronated for a long time also develop pads of fat in front of and behind the external malleoli

The *anterior transverse arch* of the foot is not a true arch but it is said to be flattened when the heads of the second to fourth metatarsals are forced downward Morton s disease or metatarsalgia The characteristic symptom is pain under the toes on walking and the pathognomonic sign is a callus on the ball of the foot High narrow heeled shoes are a fruitful source of pain They place an undue amount of weight on the base of the toes which leads to fallen anterior arches They cause the ankles to turn with each step so that they and the knees are strained They tilt the pelvis downward in front since the body must be carried backward to maintain balance and this accentuates the lumbar concavity and pronates low backache High heels are a necessity however for one whose Achilles tendons are short because normal dorsiflexion of the foot is difficult and painful

Knock knees are common in women obese persons and those with flat feet when they cause tenderness it is located just above and on the medial side of the knee joint Obesity is also the commonest cause of *lumbar lordosis* and *dorsal kyphosis* The pendulous abdomen strains the joints and ligaments of the lower lumbar region The shoulders are thrown backwards for balance which further increases the concavity of the small of the back and then the head must be thrust forward to complete the erect position of the body so that the shoulders become rounded Persons who are thin may present the same S curve if their abdominal muscles are lax for a pot belly is pendulous The recti abdominis are therefore quite properly described as the anterior muscles of the back Such back strain is obvious when the patient stands and shows prominent glutei hollow back and hunched shoulders When the condition is of long duration the back maintains the same curves when the patient sits down The lumbar curve may be maintained even when he stoops forward When he lies down the lumbar area arches above the bed unless the hips and knees are flexed

Strain due to *forward position of the head* may occur independently in those who use their necks a great deal such as school teachers book keepers and taxi drivers A long day of driving an automobile or a long evening looking up at flickering movies are frequent causes of a basal headache A low backache also follows a motor trip when the lumbar spine is unsupported and subjected to every jar the weight being carried on the ischial tuberosities and the dorsal spine If in this position one leg is extended as with the foot on the gas pedal there is a further

has a beneficial effect on coexisting arthralgias and this seems to be the most likely explanation In any event the therapeutic indications are worthwhile For example a fireman disregarded instructions as to care of his flat feet when he found that a week without three nickel candy bars daily and pie at each meal left him free from pain This improvement has continued for five years Deficiencies of vitamins and minerals were also considered to be present in 50 per cent of my cases as measured by optimum standards but here the results of adding milk and fruit were less obvious Only rarely was a case of scurvy detected by finding a history of bruising easily tenderness along the shins spongy gingival margins and a positive Rumpell Leed test Overindulgence in coffee appears to cause joint discomforts frequently perhaps by aiding insomnia and nervous tension

Menopausal Type — One third of my female patients dated the onset of the symptoms of their hypertrophic arthritis from the menopause The onset was in an indefinite three year period in those in whom the cessation of menstrual flow was natural but it was fairly abrupt in those in whom it was induced artificially by some pelvic operation This observation confirms the experience of many others yet it does not appear to be possible to isolate such cases as a very distinct group The arthritis itself is quite similar to that of other patients and of course atrophic arthritis may commence at this time also It is a time of life when fatigue and mechanical factors begin to exact their price obesity becomes prominent and family responsibilities are at their peak. An endocrine factor may be of indirect importance in the women who suffer from vasomotor instability during the process of readjustment Their hot flushes are followed by chilling sensations and these in turn by arthralgias If adequate estrogenic substance be given to control the flushes the joint pains abate in large degree although the physical signs remain and the arthropathy progresses as in all other cases

Myxedema Type — Many middle aged women put on weight easily even though they eat nothing Many of them also complain of tiring more easily than usual They suffer in cold weather They perspire little their skin is dry their hair coarse and their finger nails brittle Only relatively few however clearly show signs of myxedema in slow deep husky voice waxy induration of subcutaneous tissues especially about the face and neck pallor with little actual anemia and fat pads over the shoulders and at the base of the neck Such persons are most likely to be found in goiterous district so that the experience of all workers has not been uniform Some doubt any significant relationship between myxedema and arthritis Certainly the evi

that is meant for physical exhaustion enforces the rest which brings relief It is rather the fatigue of tired nerves that of the business man whose load is too great that of the distracted housewife of the widow whose grief is overwhelming of the person whose philosophy is unequal to the task of arriving at a satisfactory compromise between desire and reality of the person who fights middle or old age by an excess of activity and of the insomniac who reads himself to sleep Such people rarely escape tenderness or stiffness in their joints A rather young public accountant with hypertrophic arthritis of the neck once assured me at great length that he was not tired because he had many days off and always retired at ten He was cured by a vacation in the Maine woods and then came back to admit that fatigue was his only trouble He retired by going to his room where he had a swivel chair between two desks He worked at accounting problems on one until he was tired then at an architectural hobby on the other until he was convinced that bed was desirable While waiting for sleep he read a detective story and always finished it so that unconciousness came rarely before four in the morning although the day s activities began at eight In Maine there was no light at night to help him fight insomnia, and he went to sleep at dusk It has been my experience that persons who burn the candle at both ends come to grief sooner or later There are few who can get along safely with less than eight hours of bed rest every day unless they make up the deficiency by frequent vacations Nor does it seem possible to erase the fatigue caused by one activity by adding another to it It is said that mental efforts are not tiring because they require the consumption of few calories but the fact is that many minor rheumatic complaints disappear with reasonable relaxation

Malnutrition types rank third in order of frequency if obesity is included Fifty five per cent of my cases were over weight their average excess of the calculated normal being forty pounds The effects of obesity on joints are however largely mechanical Errors of diet can be responsible also for symptoms in the articular tissues of some hypertrophic patients even though the mistakes may be no different from those of normal persons Careful analysis of the food habits of my patients showed that 60 per cent of them were taking a distinct excess of carbohydrates when their feces were examined an acid reaction to litmus paper was common along with undigested starch and iodine staining organisms and when their treatment included regulation of diet the improvement that followed seemed to be attributable in part to a reduction in carbohydrates The mechanism of this association is not clear Relief of nervous indigestion and disordered action of the bowels

has a beneficial effect on coexisting arthralgias and this seems to be the most likely explanation In any event the therapeutic indications are worthwhile For example a fireman disregarded instructions as to care of his flat feet when he found that a week without three nickel candy bars daily and pie at each meal left him free from pain This improvement has continued for five years Deficiencies of vitamins and minerals were also considered to be present in 50 per cent of my cases as measured by optimum standards but here the results of adding milk and fruit were less obvious Only rarely was a case of scurvy detected by finding a history of bruising easily tenderness along the shins spongy gingival margins and a positive Rumpell Leed test Overindulgence in coffee appears to cause joint discomforts frequently perhaps by aiding insomnia and nervous tension

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dence does not permit an assumption of etiologic importance at present An association is close I believe for 149 of my patients with hypertrophic arthritis seemed to warrant a determination of their basal metabolic rate This was below −20 in 12 per cent and between −10 and −20 in another 31 per cent Seven cases had had their thyroid glands removed for hyper thyroidism and an equal number for adenomatous goiter A state of hypothyroidism has an uncertain basis for the symptoms and low metabolic rates are poor guides when taken singly But when they are taken together and there is a favorable response to small doses of the extract of the thyroid gland almost always there is benefit to the hyper trophic joints as well I have made it a practice to search for myxedema in every patient with hypertrophic arthritis who does not reveal another activating factor that explains his trouble satisfactorily It is easily overlooked yet the reward of finding it is gratifying For example a salad maker was treated in various clinics for a year as a neurasthenic because of severe arthralgias without cause When she was referred to our clinic definite hypertrophic arthritis was found and also the typical signs and symptoms of myxedema The basal metabolic rate was −31 Her joint symptoms have remained absent almost continuously for four years on thyroid therapy even though her formerly painful hands are in ice water as much as they were before

Vascular Disease Type — Varicose veins are numerous in any group of stout middle aged people The discomfort which they cause adds to the unpleasantness of stiff squeaky knees The persistent soreness about old thrombophlebitic ulcers and the heavy awkwardness of phlegmasia alba dolens also aggravate arthritic symptoms in the legs so that it is often wise to include active therapy for them in the management of the joints Blood pressures over 160 mm of mercury likewise are common in patients with hypertrophic arthritis Perhaps a third of them prove to be temporary since normal values are obtained after adequate rest Clinically important hypertensive and arteriosclerotic heart disease how ever was present in 18 per cent (87 cases) of my series Mild degrees of passive congestion can cause aches in the legs toward the end of the day and cramps in the legs at night Some relief follows rest and ad ministration of digitalis Whether this happens or not the status of the arthritis is dependent to a degree on the cardiac disease

Senile Type — With advancing years chances for trauma are accepted gingerly so that frank and disabling bouts of pain in hypertrophic joints are not common Close observation of elderly people however shows how very frequently they suffer mild discomfort from degenerative changes in joints and periarticular tissues There is stiffness after rest Motions

are slow and sometimes awkward Extra warmth and much extra rest are needed to make activity possible

Relation of Other Diseases to Hypertrophic Arthritis — Disease elsewhere in the body often serves to make the patient with hypertrophic arthritis aware of joint discomfort as has been stated already Chronic bronchitis with emphysema of the lungs and chronic peptic ulcer of the stomach or duodenum are good examples Rest is an essential feature in the treatment of each and when they are under control there is more comfort in the joints The pain of calculus in the biliary or urinary tracts may be imitated by hypertrophic spondylitis or both may exist together Procidentia may be responsible for pain low in the back and down the legs

The neuritic pains of patients with diabetes mellitus often appears to arise from hypertrophic arthritis particularly of the spine Control of the glycosuria is likely to lessen their paresthesias Herpes zoster is not a rare disease in elderly people there were 17 cases in my group Post herpetic pain that lingers for weeks and months sometimes is relieved by resting flat on the back The paresthesias of posterolateral sclerosis must be distinguished from those of hypertrophic arthritis Three cases of pernicious anemia were discovered in my clinic by noting the loss of vibratory sensation in the legs the red blood cell counts not being appreciably below normal Similar sensations are met with in cases of hypochromic anemia due to iron deficiency and in cases that resemble vitamin B deficiency In all these cases a glance at the tongue is helpful to note pallor or redness and atrophy of papillae Finally convalescence from any major surgical procedure is a popular time for previously silent joints to complain

Neuropathic arthritis described by Charcot is an extraordinary grade of hypertrophic arthritis which occurs in a few patients with diseases of the spinal cord chiefly tabes dorsalis and syringomyelia The sensation of pain is almost abolished so that the patients lack the protection of muscle spasm that follows stress and strain The result is a rather rapid degeneration of cartilage and an enormous overgrowth of osteophytic spurs With loosened ligaments tendons and capsules the joints become more and more unstable There is no ankylosis and muscle atrophy is absent Use is persisted in however awkward it may be Trophic disturbances may play a part Any joint may be affected but usually only one or two are involved Those of the legs are selected by tabes dorsalis Syringomyelia destroys higher portions of the spinal cord so that it may involve joints of the arms or spine as well as those of the legs

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years of age as to be regarded as a normal part of the ageing process It is caused by fibrillation and splitting of the shoulder capsule and the suprapsinatous tendon Since it is a hanging joint the cartilaginous surfaces are not worn away It might be more precise to term it fibrositis but its association with hypertrophic arthritis elsewhere in the body makes its inclusion in the same category proper It is the cause of paresthesias and a dragging discomfort when the arm is long unsupported or when the arm is held for a time in rotation as in sleeping with the hand under the head Local tenderness is absent unless the surrounding bursae are irritated There is little limitation of motion Spasm and atrophy of the muscles of the shoulder girdle should arouse a suspicion of atrophic arthritis

The *toes* fail to show knobby enlargements similar to the fingers although degenerative signs are visible on x ray films A *bunion* is caused by the lateral deviation of the great toe due to hypertrophic changes The *ankles* show signs of this form of rheumatism almost as infrequently as the wrists even though they are weight bearing joints Chronic *flat foot* may however show roentgenographically eburnation of bone and narrowed joint spaces The common symptomatic involvement is due to strain on muscles and tendons as has been described *Pied force* march foot is the name given to fracture of the second or third metatarsal bone near its distal end probably caused by the pull of attached ligaments and muscles while walking

The *knee* is the most active joint symptomatically in hypertrophic arthritis This is because it is used more often in weight bearing through a wider range of motion than other joints and the degenerative changes are hastened by the strain of obesity knocking bowing hyperextension by sprains of the cruciate or patellar ligaments and by tearing or dislocation of the semilunar cartilage The enlargement is only slight or moderate and the outline of the knee and of the patella is irregular Tenderness is present only on the lateral margins of the joint Function may be astonishingly good even in advanced cases save where trauma has caused a degree of fixation A twisting or a sudden motion causes pain and limitation but gentle passive motion meets little objection Crepitus is found almost invariably It is gritty crackling even audible quite distinct from the leathery rub of atrophic arthritis Synovial effusion is uncommon and temporary It comes quickly with trauma and causes the patella to float above the joint This may be difficult to demonstrate because of the associated effusion in the neighboring bursae unless the joint tissues are held firmly by two hands while the patella is pressed upon Atrophy of the quadriceps femoris is found often more

Features in Individual Joints of Hypertrophic Arthritis

Heberden's Nodes — The hard irregularities of the distal finger joints which are so common in people in the latter half of life were recognized by Heberden in 1802 as *a benign form of rheumatism distinct from gout*. They are but a part of a generalized hypertrophic arthritis although they may be its chief sign. The curious sex difference has been mentioned. Men have them less often in milder form later in life and usually with similar knobs on the proximal interphalangeal joints. Women display them first around the menopausal period in more florid and symptomatic form and without changes in the middle row of joints. Hereditary influences may be at work in those in whom they appear early in life. Such a familial trait has been reported by the several patients under thirty years of age that I have had. Their origin is more mysterious than it is for many hypertrophic joints. Exposure to cold weather and the trauma of occupation and sports is the obvious explanation for a number of cases and for a time these show the signs of active arthritis. Yet they are found fully as often in women whose hands have been protected all their lives. They may appear in one or two fingers and spread to all eight so slowly and silently that when the physician points them out the patient is surprised to see them. They may interfere scarcely at all with the comfortable functioning of the joints. Numbness tingling and blunting of the sense of touch generally occur after they have been present a long time. Dysfunction is greater where mechanical injuries have caused a degree of degeneration of cartilage but even the most distorted joints can be moved a little and are useful. In some women they grow rather rapidly and may be quite tender and even painful for a short while. Cystic swellings may protrude from the dorsolateral aspects of a few of them. They are herniations of the synovial membrane distended by effusion. At such times the overlying skin is shiny and perhaps red but tenderness is minimal. Aspiration yields a thin sterile jelly. Removal is unwise because infection is likely to be introduced and this ends in a stiff joint. The fluid is absorbed spontaneously if given time.

The *metacarpophalangeal joint of the thumb* particularly on the right hand frequently exhibits a moderate and gritty crepitus. Its range of motion is little altered. The other knuckles do not show significant degeneration. The wrists and elbows are almost never the site of hypertrophic arthritis.

A friction rub that is palpable and audible to the stethoscope is so common and asymptomatic in the *shoulders* of individuals over thirty

it to disappear Good care eliminates the fraction of stiffness that is due to muscle spasm Motion is restricted clinically at first in flexion so that the patient cannot bend over to tie his shoe or pick an object from the floor or sit with crossed knees Nor can he sit far back in a chair because his thighs must incline downwards The affected leg seems longer than the other at first when it is favored by letting it hang downward and outward In late cases actual shortening of the leg occurs due to loss in length of the femoral neck and to adductor spasm Lumbar lordosis and scoliosis is caused by this inequality in the length of the legs and by the flexion deformity for this requires the body to be thrown backwards to maintain an upright position The gait of such a person is quite revealing It is a painful or careful limp which involves little motion of the hips The knees are used to supplement the lost freedom and together with the feet they may take on an amusing appearance of ball and socket function A cane is employed to add stability for the stiffness makes sudden lifting of the feet impossible Diagnosis is made by watching the gait and the position while standing Rotation is limited first then abduction and adduction and lastly flexion and extension Pain may or may not be reported at the boundary of each action Atrophy of the buttocks is prominent The thighs are little affected

When all its joints are considered the *spine* is the commonest location of hypertrophic arthritis The sites of election are the lower cervical and the lumbar regions The coccyx and the first two cervical articulations are spared The weight bearing surfaces between the vertebral bodies are involved chiefly the facet joints much less and the costovertebral joints perhaps only in cases of pulmonary emphysema The intervertebral discs gradually lose their elasticity as middle life approaches Two results follow the loss of these shock absorbing cushions More and more weight is borne directly upon the bodies of the vertebræ and the spaces between them are lessened Since the ligaments are not diseased and since no effusion is possible due to the absence of synovial membrane there is nothing to keep the bones in their normally close alignment Abnormal mobility ensues which accelerates the grinding down of the articular cartilage at the rim of the bodies and the heaping up of interlocking osteophytes The extra pull on the tendons is reflected in the calcification which occurs at their points of attachment Such changes are greatest of course in the lumbar region where the weight is greatest and motion is in constant demand They are more conspicuous on the left side in right handed individuals X ray films show increased calcification of the bodies particularly at the eburnated joint margins

as weakness in extension than as actual loss of muscle mass Spasm of the hamstrings also is common with tenderness on the posterior aspect of the knee The symptoms rarely seem as great as the physical signs would warrant A very noisy knee may be quite comfortable Or there is pain only beyond a certain limit Characteristically the discomfort increases as the day wears on Stiffness has to be overcome in the morning or after sitting too long in one position The patient descends stairs apprehensively because the knees are loose while hanging Ascent is easier since tension guards them He arises from a chair by leaning forward and then having established a new center of gravity raising the body He falls back into a chair to avoid the strain of moving weight

Joint mice are rare but they are seldom found in any other joint than the knee They are loose bits of cartilage which roll freely between the femur and tibia Trauma may or may not be recognized as their source They are manifested by a sudden unexpected pain on motion It occurs most often in walking but may happen while turning over in bed It is relieved completely by any maneuver which allows the foreign body to slip out of the way by rest by a kick or by having the leg pulled Walking is then resumed with comfort tinged by foreboding

Malum coxæ senilis is a term long used to describe hypertrophic arthritis of the hip It is appropriate only in expressing the fact that it is usually the patient s chief disability Otherwise it is inaccurate for the patients are not senile being mostly in late middle age nor is the affection confined to one hip although perhaps in lesser degree in the other The grinding down of the femoral head and the widening of the acetabulum together with the heavy fringe of osteophytes can be caused only by long continued excessive use yet a history of more than ordinary trauma is elicited infrequently Possibly the hip was always poor mechanically due to partial dislocation or disease of the epiphysis Local pain may be very severe on motion with tenderness on pressure over the greater trochanter It may radiate to the groin or down the leg in sciatic distribution to the knee The knee may be the only site of pain so that the hip should be examined always whatever the knee discloses The pain is due to twisting or distension of the joint capsule and to muscles fatigued by the effort of guarding the joint against motion It is however of minor degree in most cases and entirely absent in not a few Morrant Baker described *cysts* which are herniations of synovial effusion outward into the buttock or onto the lateral or medial aspect of the thigh They are rare Stiffness is invariably present overuse increases it and in view of the organic changes which have advanced to a considerable degree before the patient presents himself it is futile to expect

lies supine with his thighs flexed and his knees bent the legs resting on the arm of the examining physician who swings them to either side there is pain and restriction of motion just above the sacrum This maneuver does not disturb the sacroiliac joints When the patient is prone raising the trunk or the thighs causes pain over the fourth or fifth lumbar spines

Sacroiliac arthritis is met with most often in persons of early middle age It becomes less common later on for it appears to be almost universal for this joint to fuse Before this takes place a slight degree of *motion in a lateral direction is possible If forced beyond the normal* range the rough surfaces of the sacrum and ilium lock tightly in a new position causing acute pain by pinching the soft tissues and stretching the heavy ligaments The pain is lancinating aggravated by the slightest motion and travels throughout the sciatic distribution After a few hours or days the disability wears off depending upon how rapidly restoration is accomplished Repetition invites further attacks until ankylosis is complete The sacroiliac joint is traumatized easily by awkward coordination of the trunk and legs in diving jumping or dancing or by an unexpected downward step A sudden jar as in sneezing or coughing while sitting in a half reclining posture or standing with the weight on one leg may be sufficient An automobile driver whose lumbar spine is unsupported and whose right leg is constantly extended to the gas pedal may develop chronic strain in the right sacroiliac joint The diagnosis is made easily It is observed that the patient sits or stands in such a manner as to bear the least possible weight on the painful joint Stooping is accomplished with difficulty only the normal side being employed When the patient lies supine tenderness may be found on the abdominal side of the crest of the ilium and Poupart s ligament It is due to a sensitive spasm of the iliacus muscle Since the area is close to McBurney s point acute appendicitis may be suggested Pain is not uncommon along the external femoral cutaneous nerve and into the groin Spasm of the iliopsoas muscle causes flexion and adduction of the hip and a scoliosis of the lumbar spine concave to the injured side Straight leg raising causes pain at a certain elevation because it rotates the ilium by the pull on the hamstring group This maneuver also causes pain when sciatic neuritis is present In order to distinguish between them the straight leg is elevated to a point just below the level at which pain appears and the examiner then forcibly dorsiflexes the foot The sciatic nerve thereby is put under further tension but the sacroiliac joint is unaltered If distress appears it is due to irritation of the nerve Raising the leg on the sound side causes pain in the opposite

narrowed but not obliterated joint spaces interlocking and occasionally fused osteophytes and no calcification of the anterior ligament Physical examination shows no atrophy of muscles or skin Moderate tenderness may be felt on pressure on either side of the spinous processes The symptoms are moderate in the great majority of cases Whether they last for a short time and are repeated frequently or are more persistent they do not interfere with good health

Involvement of the *cervical spine* results in a wide range of symptoms There may be a steady ache localized to the base of the skull Sharper pain may radiate about the head to the eyes or about the neck to cause a painful throat or to the shoulders and down the arms Paresthesias at the back of the neck are very common All of these distresses occur in relation to strain rather than from exposure to inclement weather They are encountered in people who use their necks most such as taxi drivers school teachers and seamstresses The tension of an emotional situation may produce them A long automobile drive or viewing a motion picture from a seat well below the screen may do so Acute torticollis is rare Its shorter attacks are due to chilling of the neck probably transient affections of the muscles and fasciæ Chronic wry neck has an arthritic basis

Arthritis of the *upper dorsal spine* is the source of much mild dis comfort about the shoulders and chest especially in persons who slouch with their heads far forward Pain may radiate so as to suggest angina pectoris for it appears with activity and is relieved by rest in a recum bent position This is to be ruled out very cautiously by proving the heart to be normal by physical examination and by noting that the pain is as often on the right side as on the left It is located superficially and may consist entirely of paresthetic sensations in contrast to the deep squeezing agony of angina *Lower dorsal arthritis* may send radiations to the chest and abdomen mimicking the pain of gall bladder disease or renal colic Pleurisy comes to mind when breathing is uncomfortable but pleurisy is rarely bilateral produces a friction rub and is not fully relieved by lying supine

Arthritis of the lumbar spine is the commonest cause of *lumbago* and a frequent cause of *sciatica* It is detected in the upper part by ob serving that when the patient stands or sits forward bending is fairly free but that when an attempt is made to regain an upright position he undertakes it cautiously and with apprehension raising the head first and then the shoulders Twisting in either direction may be stopped by pain When the patient is prone raising the head causes pain in the affected area If the lower lumbar spine is at fault then when the patient

affected joints. Roentgenographic films often are valueless, as has been mentioned, because the gross changes they reveal may be inactive clinically and because acute pain may arise in joints which they depict as fairly normal. It is of the greatest importance to distinguish it from atrophic arthritis, since the prognosis and treatment are so different. The appended table (Table I) lists many distinguishing features between the two, and in most cases no difficulty is encountered. In individual cases, however, the issues are so often confused that I find decision impossible on the first or even on several visits.

TABLE I

Constitutional Signs and Symptoms	*Atrophic Arthritis*	*Hypertrophic Arthritis*
General Health	Poor	Good
Infection	Common, occasionally focal, with effect on arthritis	Unrelated, no effect on arthritis
Weight	Loss is common	No loss, obesity common
Fatigue	According to joint disease	According to physical and emotional activity
Lymph Nodes, Spleen	Often enlarged	Normal
Tachycardia, Fever	Often present	Absent
Anemia	Occasional	Absent
White Blood Cells	Leucocytosis or leucopenia	Normal
Differential Count	Young granulocytes, relative lymphocytosis	Normal
Sedimentation Rate	Increased	Normal
Joint Signs and Symptoms		
Distribution	Symmetrical, peripheral	According to weight and use
Terminal Finger Joints	Rare	Common
Wrists, Elbows, Ankles	Common	Rare
Swelling	Fusiform	Irregular or absent
Effusion	Common, persistent	Rare, short duration
Ankylosis	Common	Absent
Atrophy of Muscles	Always	Temporary
Atrophy of Skin	Always	Absent
Periarticular Lesions	Common	Uncommon
X-ray	Decalcification, sharp irregularities	Eburnation, osteophytes

Periarticular forms of arthritis which are distinct, such as bursitis and tendovaginitis, cause little trouble in diagnosis. *Gout* is to be distinguished by its characteristic history of sudden severe attack, with complete freedom from the signs and symptoms of arthritis in the intervals for an indefinite period of years, and by the identification of tophi which contain salts of uric acid. When chronic joint changes finally appear in

sacroiliac joint by the slight twist to the pelvis that it produces When the patient lies prone elevation of one thigh exerts a torsion on the same sacroiliac joint elevation of both thighs together affects the lumbar spine alone

A short iliotibial band can strain the sacroiliac joint by tilting the pelvis downward at an angle If both bands are tight there is lordosis without scoliosis The insufficiency of this fascia can be demonstrated by instructing the patient to lie on his side with the lower leg flexed on his chest the pelvis being held at a right angle to the bed by one hand of the examiner who stands behind him With his other hand the examiner then grasps the patient s other ankle and draws the leg backward in extension Normally the patient should be able to touch his knee to the bed freely and without distress If the fascia lata is short the knee remains elevated or if it is forced down a board like mass is *felt on the* lateral surface of the thigh

Anatomical variations of the spine are a frequent cause of hypertrophic *arthritis in the lumbar region A sacralized fifth lumbar* vertebra forms a false joint between its transverse process and the sacrum which is easily strained The split spinous process in spina bifida may create an irritable contact with the next *spine If there is a* congenital defect in the arch of the fifth lumbar vertebra its body may be pushed forward out of line with the rest spondylolisthesis This does no harm in many cases but it may cause *collapse pressure on the nerve roots* between the fourth and fifth Herniation of a small portion of an intervertebral disc into the body of a vertebra is of roentgenological interest only for it seems to produce no symptoms When such a mass ruptures posteriorly it may press upon the spinal cord or cauda equina and give rise to a syndrome like cord tumor or bilateral sciatic neuritis Cases of this peculiar accident have been detected recently by locating the mass by a radiopaque oil injected intraspinally and relief has followed operative removal Ordinary films of the spine give no hint as to its presence Since this diagnostic test is not without its danger and discomfort it is *not to be advised until all the more ordinary* causes for the symptoms have been proven absent

Differential Diagnosis of Hypertrophic Arthritis

Hypertrophic arthritis usually can be seen on casual inspection Its presence in the body is safe to assume when an individual is over forty To identify it as a cause of symptoms however requires more precision Proof should include evidence of disability and distress in and from the

plaints depends upon the ingenuity of the physician and the cooperation of the patient In my clinic 135 patients failed to return for treatment Of the remaining 331 cases 53 per cent showed good results 32 per cent were improved and only 15 per cent were not helped Of the 48 failures 20 did not cooperate 18 had associated diseases that hindered progress (heart disease 5 carcinoma 4 osteomalacia 3 diabetes mellitus 2 Paget s disease 2 pernicious anemia and senile psychosis each 1) 7 were unable to rest properly and 3 had unremedied mechanical difficulties

Treatment of Hypertrophic Arthritis

Much can be done for the patient by discussing with him the nature of this form of arthritis A great cloud of fear is dispelled when he realizes that it does not cause invalidism and that it rarely cripples the joints seriously He is then more willing to accept the few simple adjustments that are necessary for comfort At least he is less likely thereafter to be a victim of unwarranted therapy

A great deal can be accomplished in preventing hypertrophic arthritis from becoming clinically burdensome This is the privilege of the family medical advisor who is in charge of the patient s health from childhood on and who is in a position to guide every aspect of his life by intelligent use of the annual physical examination There must be good care of fractures to secure normal alignment and good after care to restore function Sprains and dislocations are to be watched Early recognition of diseases of the epiphyses of bones and attention to subsequent deformities may lessen later mechanical stresses The correction of postural errors is desirable as soon as they are discovered there is no need to wait for them to cause trouble

Good advice also is in order as to the hygiene of diet rest and exercise whenever it seems to be lacking The middle aged person may need to be reminded of his expanding waistline and of the folly of continuing to order his life as if he were still young He should indulge in less strenuous competitive sports doubles rather than singles in tennis and only a foursome at golf often 9 holes instead of 18 Exercise is valuable but the sporadic resort to violent setting up exercises is stupid and *harmful* They are an excellent means of inducing an acute sacroiliac strain or of hastening the degeneration of traumatized joints Much attention should be given to the reduction of occupational hazards by means of pauses for rest a change of tasks or the protection of exposed joints by braces or leather pads

Rest is essential for those in whom fatigue is a factor It need not

gout, they partake of the features of both hypertrophic and atrophic types but the distribution of the joints the good health of the patient and the inconspicuous muscle and skin atrophy suggest the former more than the latter. Instances of *hysteria* or *malingering* are rare in my experience. They are to be suspected when the accused joints are held in excessive rigidity and often not in the position of greatest ease. The symptoms are exaggerated beyond adequate physical basis. They do not conform strictly to the usual functions of the joints. Other hysterical signs are present elsewhere.

In cases of *back pain other causes than arthritis* are to [illegible] in mind. These are rectal disorders, prolapse of the uterus, [illegible] the uterus, prostate, pancreas or rectum, malignancy [illegible] the spine, uterine fibromata, chronic pelvic inflammation, [illegible]itis or renal stone, a chronic peptic ulcer on the posterior wall [illegible] [illegible]ach or duodenum, senile osteoporosis, fracture of the body or [illegible] process of a vertebra.

The pain of *osteitis deformans* is in the affected bones due [illegible] stretching rather than in the joints.

Prognosis of Hypertrophic Arthritis

Cure of hypertrophic arthritis is impossible. The [illegible] changes in the joints are permanent. They tend to increase [illegible] time [illegible] on. The rate of progression varies largely with the manner in which the joints are used. It stops only with death, which occurs entirely uninfluenced by the arthritis, or when osteophytes have so interlocked that further joint motion is prohibited.

Cure of the symptoms which hypertrophic arthritis produces is a totally different matter. The general health is unimpaired by them. Most individuals grow old accepting the limitations imposed by the years and injuries with good grace or bad, and they suffer only minor or temporarily upsetting arthralgias. Those who suffer more invariably show sufficient cause which can be attacked with a measure of success. This is quite contrary to the situation in atrophic arthritis where the foe often is concealed, baffles one's best efforts at times and returns without warning. Minor respiratory infections which may be so serious for the atrophic patient may be beneficial to the hypertrophic arthritic if they persuade him to take a much needed rest. Symptomatic recurrences can be traced to stress or strain on the joints, to some unwholesome habit of eating, sleeping or worrying, or to some major malady in the body. How much is accomplished in the relief of the rheumatic com

plants depends upon the ingenuity of the physician and the cooperation of the patient. In my clinic 135 patients failed to return for treatment. Of the remaining 331 cases 53 per cent showed good results, 32 per cent were improved and only 15 per cent were not helped. Of the 48 failures 20 did not cooperate, 18 had associated diseases that hindered progress (heart disease 5, carcinoma 4, osteomalacia 3, diabetes mellitus 2, Paget's disease 2, pernicious anemia and senile psychosis each 1), 7 were unable to rest properly, and 3 had unremedied mechanical difficulties.

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A great deal can be accomplished in preventing hypertrophic arthritis from becoming clinically burdensome. This is the privilege of the family medical advisor who is in charge of the patient's health from childhood on and who is in a position to guide every aspect of his life by intelligent use of the annual physical examination. There must be good care of fractures to secure normal alignment and good after care to restore function. Sprains and dislocations are to be watched. Early recognition of diseases of the epiphyses of bones and attention to subsequent deformities may lessen later mechanical stresses. The correction of postural errors is desirable as soon as they are discovered; there is no need to wait for them to cause trouble.

Good advice also is in order as to the hygiene of diet, rest and exercise whenever it seems to be lacking. The middle aged person may need to be reminded of his expanding waistline and of the folly of continuing to order his life as if he were still young. He should indulge in less strenuous competitive sports, doubles rather than singles in tennis and only a foursome at golf, often 9 holes instead of 18. Exercise is valuable but the sporadic resort to violent "setting up" exercises is stupid and harmful. They are an excellent means of inducing an acute sacroiliac strain or of hastening the degeneration of traumatized joints. Much attention should be given to the reduction of occupational hazards by means of pauses for rest, a change of tasks, or the protection of exposed joints by braces or leather pads.

Rest is essential for those in whom fatigue is a factor. It need not

be so confining or so long in duration as for the patient with atrophic arthritis Eight or ten hours in bed at night may be enough More important is a nap in the afternoon which breaks the day s activities in two and lessens the accumulation of fatigue in the evening If this is not consistent with the performance of necessary duties — and the treatment seldom needs to interfere with them — then it is always pos sible to take a few short periods of relaxation during the day whether it be at home in an office or in an automobile Another alternative is a short vacation or a simple change of scene or pace Relief from chronic insomnia is to be sought not in reading or working or in sedatives but in going to bed early not too tired with reliance on inner resources for entertainment until unconsciousness comes

Rest must be obtained also for painful joints The fallacy of lim bering up has been pointed out It is true that this overcomes muscular stiffness and decreases traumatic effusion for the time being but it does so at the expense of further injury to articular structures Only when wear and tear are avoided is repair possible When this is complete the joints are as free as their osteophytes permit Such rest is to be pro vided by strict attention to the needs of the particular joints A painful neck can rest only without pillows If extension is distressing it may be maintained for several short periods during the day and night Occa sionally a stiff collar of cardboard sheet wadding and a towel may be made to transfer the weight of the head directly onto the shoulders and secure immobility Extension is required also for dorsal arthritis aided perhaps by a small pillow under the shoulders Lumbar backache is relieved when that portion of the back is flat with the hips and knees lying flexed over a large pillow In some cases a small pillow filling the lumbar curve feels comfortable A similar position can be used for sacroiliac strain In both instances the dorsal and cervical portions of the spine must be flat also the floor can be used if the bed does not have stiff springs or a piece of wallboard may be inserted under the mattress The jars of riding in an automobile can be lessened by sitting forward with flexed knees or by placing a pillow at the small of the back For acute sacroiliac arthritis a belt of canvas three or four inches wide may be pulled tightly around the pelvis in such a position that the grip comes just below the anterior superior spines of the ilia Strapping with adhesive tape controls the situation for a few days but is irritating to the skin if used for longer periods For more severe and chronic cases extra rest and a well made sacroiliac belt are desirable The use of corsets and braces is a matter for orthopedic surgeons to settle

A recumbent position is necessary to put arthritic hips at rest In some cases they may be spared by leg irons which extend from the ischial tuberosity to the heel of the shoe A cane is accepted more readily A bandage of elastic cloth six inches wide affords excellent protection to swollen tender knees Simple cases of flat foot strain may need only walking with the feet parallel for relief More resistant cases do well with a wedge of leather added to the medial and forward position of the heel It should not be more than a quarter of an inch high Arch supports are best when made to measure for the individual requirements of both the longitudinal and transverse arches A little ingenuity is all that is required to meet these and other local problems inexpensively and satisfactorily

Exercises are particularly helpful in correcting faults of posture They are to be used in sensitive joints not beyond the boundary of pain in order to improve their stability by muscular control For example the feet are strengthened by grasping with the toes and pulling medially by walking with the toes clenched or pigeon toed The knees respond to tightening of the patellae known as quadriceps setting The hips improve by tightening the gluteal muscles and by rotation and abduction of the thighs while lying down The iliotibial band is stretched by leaning straight legged toward a wall while standing sideways and about two feet away braced by one hand An excessive lumbar curve is reduced by tightening the glutei to level the pelvis raising the chest and pulling in the abdomen Exercises for breathing and for improving abdominal muscles are important aids to posture

Much can be done indirectly for mild persistent arthralgias by an optimal *diet* and regular unhurried meals An excess of pastry tea coffee and tobacco is to be avoided Instructions as to food need to be as specific as in atrophic arthritis for the same fads and fears are encountered The reduction of obesity obviously is important It is to be undertaken with balanced rations slowly at a rate not to exceed four pounds a month or forty pounds in one year The temptation to overeat is lessened by eating the full amounts permitted and by resting before meals Many excessively obese individuals do well to maintain their weight at a level distinctly above the average normal for their height and age for a long time before accepting the need for further loss because they are healthier and heartier so The cure of intestinal distress and the making regular of bowel function without stimulation also add to the comfort of the rheumatic patient

Heat is very pleasant on hypertrophic joints The hot water bath warm clothing and bed coverings are sufficient in most cases Radiant

lamps diathermy and hot boxes are entirely unnecessary but they do not appear to do harm The heat is to be placed next to the offending joint which of course may not be the site of the pain

Physiotherapy is said to work miracles at times Like miracles, proved instances are rare It is of undoubted benefit if done skillfully with special knowledge and training as to how and when to do manipulations Massage should be gentle and superficial Trauma to the joints is to be avoided Hydrotherapy is good and can be fairly vigorous in mild cases

Drugs —Acetyl salicylic acid (aspirin) is the best and simplest analgesic It should be administered as indicated in severe pain and in cases where pain prevents sleep It is unnecessary in the great majority of cases Its use is indeed unwise if it destroys the patient s guide to the necessity for rest and avoidance of overuse of joints No other drugs are of proved value in hypertrophic arthritis Remedies for associated conditions are helpful The proper treatment of anemia whether hyperchromic or hypochromic and even of slight degree may aid in dissipating paresthesias Preparation of vitamins are harmless and may be used if the spiritual support of pills is required Thyroid gland extract is indicated only in cases of myxedema where however it is of great value in controlling rheumatic tendencies Its dose should be small one half to three fourths of a grain (30 to 45 mgm) of the dried gland daily and extra caution is necessary in the elderly and in those with heart disease Digitalis appears to be of distinct aid in the minor arthritic complaints of patients with cardiac hypertrophy regardless of heart failure Estrogenic substances parenterally in large doses weekly for several months serve to control menopausal distresses

Since *foci of infection* do not contribute to the development of hypertrophic arthritis their removal has no beneficial effect on joints Too much surgery on the mouths and throats of people of middle and old age may interfere with their general health and the acceptance of a normal diet Vaccines and injections of foreign protein are useless in this type of arthritis

Surgery offers much in particular instances Bloody effusions in traumatic cases require aspiration and lavage to prevent adhesions Joint mice may have to be removed Fusion may be induced in the sacroiliac joint or the hip or knee if conservative measures fail to control pain A short iliotibial band can be lengthened by dividing it near its origin at the crest of the ilium The indications for arthroplasty and other procedures are best left to the judgment of a conservative orthopedic surgeon

Diagnosis and Treatment of Periarticular Forms of Arthritis

Any discussion of arthritis is far from complete when the two main types of intra articular lesions have been reviewed for there are several affections of the periarticular tissues which appear to be closely related to them and yet to exhibit a certain independence clinically They greatly exceed joint disease in numbers They are often transient Usually they upset the general health very little Mechanical stresses and strains form the important part of their background Thus they are allied more with hypertrophic arthritis than with the atrophic forms and of course degenerative joint changes become manifest in the patients sooner or later Since their implications and therapeutic demands are different it seems wise to consider them separately

Bursitis

Multiple inflammatory bursitis is part of atrophic arthritis Gout also appears in many bursæ When one or two bursæ are painfully involved the affection may be a distinct entity Trauma in some form and degree is the only necessary etiologic agent Infection rarely is proved nor has any toxin been demonstrated save lead in the few cases of plumbism These are acute and chronic forms which are differentiated by the severity and duration of symptoms and by the alterations in the bursæ Acute bursitis shows more outpouring of synovial transudate Chronic bursitis is characterized by less effusion and more thickening of the walls by connective tissue which may change into fibrocartilage or bone The capsule of a joint tendons muscle and nerve sheaths which form the boundaries of the bursa always are torn ruptured thickened or sclerosed Calcium sometimes is deposited in the walls or in the exudate as a creamy paste It may disappear spontaneously

The *symptoms of bursitis* occur in people who are in good health There is no fever weight loss atrophy of skin or bone malaise or leucocytosis Tenderness is located directly over the bursa and nowhere else It may be absent in chronic cases Pain is experienced on any motion which disturbs the muscles nerve sheaths and tendons about the bursa and radiates throughout their extent In acute cases it may be so severe as to require morphine If there has been trauma the symptoms do not subside after the local bruise has had time to heal Chronic cases suffer more from persistent soreness and paresthesias than from pain Whether or not swelling is observed depends on the situation of the

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surface and can be seen on x ray films Whether the reaction be acute or chronic trauma is the inciting agent It may be a fall on an out stretched arm or it may be long overuse in baseball or golf or with a pneumatic drill or it may be overuse at a mechanical disadvantage as when the shoulders are slouched and the head far forward The diag nostic sign of subdeltoid bursitis is inability to abduct and externally rotate the arm When such an attempt is made it falls short of a right angle even with the aid of the scapula which moves with it But rota tion is fairly free if the elbow is supported showing that the joint itself is clear The arm is held by choice in inward rotation close to the side A tender area may be palpated over the acromion process and there is some atrophy of the deltoid and supraspinatous muscles In long standing cases there may be little tenderness or pain or limitation of function These are replaced by crepitus over the shoulder and an aching soreness near the elbow when the arm hangs down Acute cases last an average of six weeks In treatment comfort is best secured in a recumbent position without a pillow the arm being held in as much abduction as possible by a pillow between it and the body During this time heat can be applied at regular intervals and supervised exercises are carried out When the patient is up he should sit in an armchair or walk with his arm in a sling fashioned so that the weight is well distributed over the opposite shoulder

Olecranon bursitis is common in miners The mass is excised easily if so desired Radiohumeral bursitis in tennis players persists a long time and is said to be hard to remove surgically Bursitis in the region of the hip may reveal no local sign It is to be suspected when there is pain and functional disability in the hip without evidence of arthritis A bursa over the ischial tuberosity may grow to large size in those who sit cross legged at work hence the name weaver s bottom Prepa tellar bursitis has been named housemaid s knee or nun s knee Adventitious bursæ may appear anywhere in response to friction or pressure as on a bunion Bony spurs not infrequently are seen on x ray films of the os calcis in persons who walk a great deal Often they are asymptomatic Gonorrhea is the cause of a few of them When they are painful (policeman s heel) a bursa is found to be interposed be tween the spur and the skin which can be protected or excised

Tenosynovitis

Effusion into tendon sheaths may be seen in tuberculosis in children occasionally In adults without these diseases it is seen as a reaction to

bursa Superficial tumors are obvious those in the hip and shoulder are readily masked There is stiffness and spasm of the surrounding muscles whose motion thereby is abolished or greatly limited This may amount to little in the indolent cases and it is more selective less general, than it is in intra articular inflammations

The *diagnosis* is simple in most cases if the disorder is kept in mind Atrophic arthritis is distinguished by fusiform joint swellings by atrophy of skin muscles and bones and by general malaise Hypertrophic arthritis may be seen on physical examination but it is relieved readily of responsibility for the symptoms Multiple neuritis may be suggested at times but its peripheral nerve lesions are not limited to those which traverse the diseased bursa Lead poisoning is shown by a gray or blue black line at the gingival margins and by paralysis rather than spasm

Treatment in general is planned as in hypertrophic arthritis Little confinement to bed is needed save for severe acute cases Local measures such as slings adhesive or elastic bandages are sufficient to put the bursa at rest Active exercises should be directed at the earliest possible moment up to the point at which pain appears Passive motion does harm if it tears or fractures the affected tissues still more Light massage often is pleasant Heat is excellent It may be dry as from lamps or a hot water bottle or electric pad or wet in the form of hot flaxseed poultices or cloths soaked in hot solutions of magnesium sulphate Medicated mud has an attraction for some people Salicylates control the pain in all but the severest cases Vaccines are valueless Removal of a focus of infection is reported on rare occasions to have worked a miraculous cure Almost always such surgery is useless and merely upsetting Resumption of normal activity of the affected part is undertaken slowly and cautiously Not infrequently excision of the bursa or its open drainage or its irrigation with saline solution are indicated to shorten the course of the disease and complete the recovery They perform these tasks admirably but a quantum of permanent change in the periarticular tissues remains and is added to what is later called hypertrophic arthritis Roentgenotherapy is said to be helpful

Bursitis of the shoulder is the most important common example The synovial membrane here covers an area of considerable extent over the capsule of the joint and beneath the deltoid muscle It is called either subdeltoid or subacromial bursitis for there is no clear division between the two portions The capsule is thickened The supraspinatous tendon is always and the biceps usually interrupted in part The insertion of the deltoid in the humerus is infiltrated with fibrous tissue and calcium Occasionally calcium is spread over the whole synovial

surface and can be seen on x ray films Whether the reaction be acute or chronic trauma is the inciting agent It may be a fall on an out stretched arm or it may be long overuse in baseball or golf or with a pneumatic drill or it may be overuse at a mechanical disadvantage as when the shoulders are slouched and the head far forward The diag nostic sign of subdeltoid bursitis is inability to abduct and externally rotate the arm When such an attempt is made it falls short of a right angle even with the aid of the scapula which moves with it But rota tion is fairly free if the elbow is supported showing that the joint itself is clear The arm is held by choice in inward rotation close to the side A tender area may be palpated over the acromion process and there is some atrophy of the deltoid and supraspinatous muscles In long standing cases there may be little tenderness or pain or limitation of function These are replaced by crepitus over the shoulder and an aching soreness near the elbow when the arm hangs down Acute cases last an average of six weeks In treatment comfort is best secured in a recumbent position without a pillow the arm being held in as much abduction as possible by a pillow between it and the body During this time heat can be applied at regular intervals and supervised exercises are carried out When the patient is up he should sit in an armchair or walk with his arm in a sling fashioned so that the weight is well distributed over the opposite shoulder

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injury which sometimes appears rather inconsequential Laborers and athletes are affected most often The diagnosis is made easily on the appearance of an elongated softly fluctuant mass which rolls freely under the skin in the situation of a tendon A leathery rub may be felt on motion if it has been present for some time The wrist particularly the extensor surface is the commonest location Tenosynovitis causes little disability or tenderness Treatment is unnecessary beyond reasonable avoidance of use until the fluid is absorbed If symptoms or impatience interfere the tendon sheath may be incised

A snapping finger or *trigger finger* is a curious affection due to a nodular thickening on a tendon as a result of injury A flexor tendon at the metacarpophalangeal or proximal interphalangeal joint is the usual site Motion is free to a certain point and then is suddenly interrupted by a snap which is more alarming than painful Return motion is impossible until the joint is unlocked by shaking the hand or pressing the finger so that the thickened area can slip past the joint or the narrow place in the tendon sheath It may heal by neglect or recovery can be hastened by immobilizing the finger with a simple tongue depressor splint for several weeks In some cases it is justifiable to open and enlarge the sheath or to excise the nodule

A *ganglion* or weeping sinew appears to be a localized tenosynovitis or perhaps a herniation of synovia from a joint It is found on the dorsal surface of the wrist more than any other place It lasts for months or years and rarely causes the slightest distress

Fibrositis

Fibrositis or muscular rheumatism is a term which is used to describe a common but little understood group of conditions characterized by stiffness or soreness in the muscles Whatever joint abnormalities are found are hypertrophic in type and they appear to have no part in the symptoms The affections are for the most part so mild that there is little opportunity for or interest in studying the tissue changes which take place Infection seems to have no connection with them Chemical alterations may cause some of the more transient attacks It is known for example that an excessive loss of water and salt is responsible for cramps in the muscles of stokers and others who work in hot atmospheres Persistent symptoms more probably are based on fibrous tissue over growth in muscles due to stress and strain over a long period of time A muscle bruise which consists of innumerable hemorrhages into ruptured cells repairs incompletely Muscle cells are replaced by fibrous tissue

and calcium may be deposited as in myositis ossificans Function is regained almost wholly but the normal architecture of the bundles is not The most benign cases of muscular rheumatism are those which come from unaccustomed exercise After the first set of tennis or game of ball or gardening chores there is an aching stiffness in the muscles employed which wears off in a few hours and is less and less evident as the exercise is continued Performance and general well being are im proved by such a period of training in young people but in older people recovery is much slower Elasticity is said to be lost and more chronic rheumatism may follow Farmers laborers and particularly miners are the usual sufferers Discomfort is experienced only with intercurrent sprains and contusions They describe their disability more as morning stiffness a loss of suppleness or a state of being muscle bound Subcu taneous nodules are visible or palpable in some cases along the spine or near the elbows Elderly individuals are affected similarly without a history of trauma so that the cause of senile fibrosis is to be sought in senescence and perhaps deficient circulation Peripheral arteriosclerosis may account for cramps in the leg Cerebral arteriosclerosis results in *the fibrillary twitchings the rhythmic purposeless movements and the* rigidity of expression which constitute a type of paralysis agitans It sometimes appears that a moderate hypertension lessens these symptoms in the aged and hypotension increases them but there are many ex ceptions In all these cases the only treatment required is reasonable rest and adequate warmth Hard laborers wear heavy underclothing from choice rather than from habit The elderly bask in hot weather and demand temperatures of 80 F or more in the winter A hot bath and a good night s sleep help to dissipate attacks in younger persons Water and salt should be consumed in liberal quantities by active workers

Insufficiency of the iliotibial band described under hypertrophic arthritis as one cause of lordosis and low backache is an example of fibrositis not associated so far as known with changes in muscles Minor degrees of it are discovered very often and appear to cause little trouble

A progressive contracture of the palmar fascia which bears Dupuy tren s name is another example This is a curious affection which is not at all uncommon in elderly individuals Its origin is obscure Mechan ical forces are not evident it is found among laborers and the white collar class alike Heredity is noted in some Men are affected nine times more than women exactly the reverse of the ratio that holds for Heberden s nodes It is always bilateral though the degree of deformity varies being greater in the right hand in right handed persons Trophic

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A *ganglion* or weeping sinew appears to be a localized tenosynovitis or perhaps a herniation of synovia from a joint It is found on the dorsal surface of the wrist more than any other place It lasts for months or years and rarely causes the slightest distress

Fibrositis

Fibrositis or muscular rheumatism is a term which is used to describe a common but little understood group of conditions characterized by stiffness or soreness in the muscles Whatever joint abnormalities are found are hypertrophic in type and they appear to have no part in the symptoms The affections are for the most part so mild that there is little opportunity for or interest in studying the tissue changes which take place Infection seems to have no connection with them Chemical alterations may cause some of the more transient attacks It is known for example that an excessive loss of water and salt is responsible for cramps in the muscles of stokers and others who work in hot atmospheres Persistent symptoms more probably are based on fibrous tissue overgrowth in muscles due to stress and strain over a long period of time A muscle bruise which consists of innumerable hemorrhages into ruptured cells repairs incompletely Muscle cells are replaced by fibrous tissue

CHAPTER XVI

DISEASES OF THE BONES

By ARTHUR GROLLMAN

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lesion in the brachial plexus might be considered for this reason All the cases that have come to my attention have been stoop shouldered the head being thrust forward The ring finger is first affected then the third and fifth are involved never the thumb or index finger Flexion is free but there is increasing difficulty with extension The joints and tendons escape The fingers are straight or flexed at the proximal joints The skin is tightly adherent and drawn into folds Slow progression is the rule There is no pain Clumsiness is the only complaint Treatment is unsatisfactory Passive or active exercises prove useless and surgical removal often fails

Finally there are the *myalgias* due to exposure to inclement weather Incurable displeasure with climate is characteristic of many arthritic individuals but acute severe muscular pain occurs quite independently of joint disease Trauma is absent The symptoms are unlike la grippe and no infection is found The general health is not altered The attacks last only a few hours or days Cure is prompt and complete so that we are left to speculate on some transient chemical or physical alteration in the muscles or connective tissues brought on by chilling In wry neck there is sharp pain on motion in one direction The head is carried in spasm towards the affected side and the shoulder rises to meet it It comes on in the morning after sleeping with the neck exposed or it appears shortly after sitting in a cold draught It subsides with heat and activity

Pleurodynia is a similar painful affection of the intercostal muscles which makes breathing agony for a short time It is relieved by heat in a recumbent position Pleurisy is absent It is distinct from epidemic pleurodynia *Lumbago* a name which too often signifies pain in the small of the back from any cause sometimes comes from a chill while lying on a cold damp surface or sitting in a cool breeze when overheated by exercise It is described as a crick or a catch It does not radiate but bending is accompanied by a groan The time honored remedy is a porous plaster or a mustard plaster which provides counter irritation but heat in any form and exercise are effective Salicylates are helpful A carthartic often is administered although there seems to be no indication for it Diagnosis is simple Organic disease in the back easily is ruled out No sign of upper respiratory infection is seen Active infestation with trichinæ which may cause confusion in diagnosis reveals painful areas in muscles elsewhere and there is an eosinophilia in the blood stream

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PART I

GENERAL CONSIDERATIONS

INTRODUCTION

The bones like other tissues are subject to almost any disease with which man may be afflicted Infections (tuberculosis syphilis etc), neoplastic growths (benign or malignant) neurotrophic disorders toxic agents (particularly lead, radium, fluorides or benzol derivatives) and metabolic disorders (as in the xantho matoses) may involve the bones as described in the sections dealing with these disorders Disease of the kidneys[4] by altering the mineral metabolism and the acid base balance as well as various chronic disorders which affect growth, may result in marked deformity of the skeleton as their principle manifestation (com pare Chapter on Dwarfism in Oxford Medicine Vol III Chapt XIX)

Diseases of the endocrine organs[6] frequently induce marked changes in the skeleton Thus, pituitary or thyroid deficiency may result in dwarfism Hyper thyroidism and Cushing s syndrome may be accompanied by pronounced osteo porosis Hyperparathyroidism is responsible for osteitis fibrosa cystica, von Recklinghausen s disease of bones described in Oxford Medicine, Vol III Chapt XV Diseases of the Parathyroid

The present chapter is devoted to a group of diseases in which the bones ap pear to be the primary site of the disorder In addition, several conditions, such as fibrous dysplasia of bone and hyperostosis frontalis interna in which the bone changes are pathognomonic of a more generalized disorder are considered

There is a large group of rare diseases involving the skeletal system, which are described in Chapters XLIII XLIII–A and XLIII–B of Vol V of the Oxford Medicine These include osteosclerosis (marble bones) arachnodactyly, arthro gryposis multiplex congenita Morquio s disease hereditary arthrodysplasia with dystrophy of the nails hypertelorism Bruck s disease hereditary enlargement of parietal foramina cleidocranial dysostosis, acrocephalosyndactylism and allied conditions craniofacial amphiarthrosis acrocephaly dystrophia periostalis hyper plastica familiaris, gargoylism acromicria, leontiasis ossea, hemiatrophy and hemi hypertrophy

BONE AS A LABILE BODY TISSUE

We customarily think of the bones as rather firm structures constituting the framework of the body which except in disease, maintain the rigid stability which

we associate with the calcareous mass comprising the isolated skeleton This view however is erroneous The osseous system instead of being an inert concretion is an exceedingly labile tissue which at all times is in equilibrium with the body fluids [a] The mineral elements of the bones enter into solution in the body fluids constantly being replaced by other elements derived from the same fluids The concept of this dynamic equilibrium was expressed first by Cohnheim many years ago and has received direct experimental verification through studies with radioactive phosphorus[1 28] When this isotope is injected and its distribution in the body subsequently determined it can be demonstrated that there is a rapid turn over of the inorganic constituents of the bones Thus it is evident that changes in the bones may be brought about by alterations in the composition of the blood and that the skeleton may reflect abnormalities in the activity of other organs and tissues as well as in the general health and nutrition of the body

The Composition and Growth of Bone

The bones are composed of an organic matrix in which the mineral salts are deposited The organic matrix is similar in its composition to the connective tissue and cartilage found elsewhere in the body and con s of collagen a glucoprotein and osseoalbuminoid Normal mature bones are composed of 50 per cent water and as much as 24 per cent fat The dried fat free material consists of 30 to 40 per cent organic matter the remainder being a complex salt mixture[1]

The exact composition of the mineral element of bone has been the subject of much study Analytical findings conform to the empirical formula $n\ Ca_3(PO\ )$ CaX where n varies between 2 and 3 and X may be carbonate oxide fluoride chloride or sulfate The inorganic salt of bone thus resembles in its composition the mineral apatites and is probably a solid solution of multiple apatites X ray diffraction studies show the bones to have an atomic arrangement similar to that of podolite a mineral of the apatite series About 99 per cent of the total calcium 70 per cent of the phosphorus and magnesium and small amounts of the sulfur sodium and chloride of the body are found in the skeleton

Ossification the deposition of the mineral constituents of the bone into its organic matrix occurs according to two types intramembranous and intracartilaginous or endochondral The membranous bones comprise the cranial vault and mandible the cartilaginous bones those of the torso and extremities Growth in length of the long bones occurs by *the continuous proliferation of cartilage cells* arranged in orderly columns in the epiphyseal cartilage This is a narrow plate supported by transverse trabeculae and penetrated by capillaries which enter it on the diaphyseal border Simultaneously with the epiphyseal growth of the cartilage there occurs a degeneration of the matured cartilage cells on the diaphyseal

end The spaces thus left by the degenerating cartilage cells are invaded by capillaries and osteoblasts or bone forming cells, which deposit the mineral matrix Normal ossification and growth of bone thus involves the deposition of salts in an organic matrix in the provisional zone of calcification at the epiphyseal diaphyseal junction with the simultaneous renewal of the cartilage at the other end of the epiphysis[1]

The hardness strength and rigidity of a bone depends on the proportion of its organic and inorganic constituents and on the intimate structure in which they are present A reduction in mineral content with a normal organic matrix will result in a soft bone as in osteomalacia which will become deformed but need not be unduly brittle On the other hand, a normal or even excessive mineral content of the bone may be accompanied by great brittleness, as in marble bones, if the organic matrix and normal deposition of the calcareous elements are defective

Metabolism of Calcium

Calcium plays an important role in the body economy not only as a constituent of bone but also in the coagulation of blood and in maintaining normal membrane permeability and neuromuscular irritability Bone diseases associated with alterations in the ionic calcium content of the blood consequently will manifest themselves often by symptoms referable to the neuromuscular system before marked changes in the bones are evident This is the case, for example, in osteitis fibrosa cystica due to hyperparathyroidism or in tetany

Calcium is the mineral present in largest amount in the body approximately 2 per cent of the body weight being comprised of this element This calcium is derived from a variety of foods The availability of the calcium in foods varies greatly, depending upon the age of the individual, the form in which the calcium is present the hydrogen ion concentration of the gut[14] the amount of vitamin D available and the nature of the other constituents present in the diet

The absorption of the calcium takes place from the upper part of the small intestine especially from the duodenum It is excreted from the large bowel so that even during starvation or on a calcium poor diet calcium is lost from the body Hypermotility of the bowel as in hyperthyroidism thus will reduce the amount of calcium available to the body The presence of fatty acids as in sprue will result in the formation of insoluble calcium soaps and prevent the absorption of the normal amount of calcium An excess of phosphorus in the diet also will reduce the availability of the calcium due to the formation of insoluble calcium phosphate Excessive fat or phosphates in the gut may even cause the loss of a greater amount of calcium from the body than is ingested

Only a relatively small proportion of the total calcium ingested is retained by

the body Thus children who are saturated in advance with calcium will absorb about 20 per cent of the calcium present in milk or in dicalcium phosphate adults about 15 to 35 per cent [16] Acidity in the gut favors the retention of calcium alkalinity retards it Hence the addition of orange juice citric acid, lactose or citrate mixture increases the calcium retention about 9 to 16 per cent [3] Ascorbic acid exerts no influence on calcium retention but vitamin D is an important factor in increasing the utilization of calcium and phosphorus as discussed later

The human adult generally is stated to require about 0 8 gm of calcium daily to maintain calcium equilibrium about 9 2 to 10 7 mgm per kilogram of body weight[18] Children previously on diets containing liberal amounts of calcium require 32 to 35 mgm of calcium per kilogram of body weight an amount represented by about a pint of milk daily [7]

The trabeculae of the bones acts as a store of calcium which may be utilized when the exogenous sources of calcium are deficient or when an increased rate of excretion of this element as in renal disease occurs The organism thus possesses a remarkable adaptability which makes it possible to maintain a normal calcium ion content of the blood even on a very deficient calcium intake Under such conditions the parathyroid glands become hypertrophied but whether the observed demineralization is due to hyperactivity of these glands or whether the observed hypertrophy is secondary to the disturbed mineral metabolism is still a matter of controversy

A normal adult on an ordinary diet will excrete 0 4 to 0.8 gm of calcium in the feces daily and 0 1 to 0 2 gm about one fourth of the total, in the urine During growth or pregnancy in acromegaly or after being on a deficient diet the individual will show a positive calcium balance that is the amount of this mineral ingested will exceed the total amount excreted On the other hand in rickets celiac disease sprue osteomalacia hyperparathyroidism hyperthyroidism or starvation one observes a negative calcium balance that is the loss of a greater amount in the excreta than is ingested the net loss from the organism being derived from the bones which become demineralized

Phosphorus Metabolism

Phosphate and carbonate constitute the principle anions of bone The phosphate radicle plays an important role in protein carbohydrate and fat metabolism and is a constituent of many of the organic substances in the animal body About 70 per cent of the phosphorus retained in the body is incorporated as calcium phosphate in the bones the remainder serving for the other functions with which this element is associated Phosphate because of its buffering capacity also

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quirement is believed to be about 400 units, but twice this amount is required during pregnancy[13]

Phosphatase Enzyme Activity

The enzyme phosphatase plays an important role in the deposition of bone, and the determination of its concentration in the blood plasma aids in the differential diagnosis of bone diseases when considered in conjunction with other biochemical analyses Phosphatases are enzymes present in the blood and tissues which hydrolyze the organic phosphorus containing esters primarily hexosemono phosphate and glycerophosphate thereby liberating the phosphate ion A variety of such phosphatases are present in the organism being differentiated from one another by the pH ranges at which each is active[1] Of particular clinical interest are (1) the alkaline phosphatase which has its optimal activity at pH 9 3 and (2) the acid phosphatase with optimal activity at pH 5 0 The former is present in the blood in bone ossifying cartilage kidney intestine, lung etc the latter in the blood prostate liver kidney etc The phosphatase activity is determined by incubating a solution of glycerophosphate as substrate in a solution buffered at pH 9 3 or 5 0 depending upon whether one is determining the alkaline or acid phosphatase respectively with the test material for one hour at 37 C The amount of phosphoric acid set free is a measure of the phosphatase activity which is expressed in a variety of units the most widely used being that of Bodansky[1] The Bodansky unit is defined as the phosphatase activity resulting in the liberation of one milligram of phosphorus in the form of phosphate from a substrate of sodium β glycerophosphate during incubation for one hour at 37 C at a pH of 8 6

The alkaline phosphatase of the blood is believed to be derived from the osteoblasts proliferating cartilage and the cells of the inner layer of the periosteum The enzyme undoubtedly plays an important role in calcification by making available inorganic phosphate for this process

The Chemical Findings of the Blood in Bone Diseases

Laboratory procedures play an important role in the diagnosis of bone disease Of these the x ray plays a preeminent role and in many cases suffices to establish the diagnosis The chemical findings in the blood and excreta also are valuable procedures which in conjunction with the clinical and roentgenological studies aid in the differential diagnosis

In Table I are collected data on the blood serum calcium inorganic phosphate and phosphatase and the excretion of calcium in the common diseases of

plays an important role in acid base regulation By its control over the excretion of phosphate the kidney effects this regulation Renal dysfunction, by failing to excrete phosphate thus will affect indirectly the acid base balance, calcium metabolism and ultimately the bones

An adult consumes about 11 mgm of phosphorus per kilogram of body weight of which only mgm are retained When present in excessive amounts in the diet, phosphate causes an increased excretion of calcium in the feces Contrariwise an excess of calcium will decrease the availability of the phosphorus and cause its excretion through the gut instead of through the urine The ratio of calcium to phosphorus in the diet thus is important in determining their utilization The normal adult human requirement for phosphorus is about 0 9 gm , but larger amounts 1 3 gm usually are ingested[10] The type of diet will however, greatly influence the amount absorbed For example, whereas 55 per cent of the phosphorus in human milk is retained by an infant, only 25 per cent of that present in cow s milk is utilized [7] About 60 per cent of the total phosphate is excreted in the urine This urinary output is increased with decreased calcium intake It is decreased where there is renal impairment, e g in chronic glomerular nephritis the fecal output being correspondingly increased It is increased in hyperparathyroidism, hyperthyroidism or when vitamin D is ingested in excessive amounts

Vitamin D and the Skeletal System

Vitamin D plays a fundamental role in maintaining the normal integrity of the skeletal system A deficiency of this vitamin during the period of growth leads to rickets during adult life to osteomalacia Vitamin D apparently is essential for the normal absorption and utilization of calcium and phosphorus, its administration affecting markedly the absorption of these elements However, this increased absorption alone is not sufficient to account for the function of the vitamin as has been demonstrated by studies with radioactive phosphorus The effect of vitamin D on the absorption of calcium and phosphorus is in large part, if not entirely secondary to its primary influence on the utilization of these elements By its action vitamin D not only induces a more economical utilization of calcium and phosphorus but also tends to overcome the inefficiency of any undesirable ratio of these elements

The usual requirements of the organism for vitamin D are obtained from natural foodstuffs or from the action of sunlight on precursors of the vitamin present in the skin When used for prophylactic and therapeutic purposes, the vitamin is obtained from fish oils and by the irradiation of ergosterol calciferol or vitamin D_2 or 7 dehydrocholesterol or vitamin D_3 The daily adult human re

conditions in which the total calcium level is altered Hyperparathyroidism and tetany are notable exceptions in which the ionized fraction is increased and decreased respectively The remaining 40 to 55 per cent of the calcium 4 0 to 5 0 mgm per 100 c c is non diffusible being combined with the blood albumen in the form of a colloidal complex[11]

The constancy of the diffusible ionic fraction of the calcium and the variability in the non diffusible protein bound fraction explain the variation observed in the total calcium content with changes in the protein content of the blood Thus the total calcium content may be elevated in multiple myeloma or in metastatic carcinoma of bone due to the hyperproteinemia present in these conditions On the other hand a calcium level well within the normal range may be of definite pathological significance in the presence of an abnormally high or low protein level[11]

In the presence of an elevated inorganic phosphate level of the blood, due for example to renal insufficiency, a depression of the calcium level below its normal level also does not have its usual significance as regards the existence of disease of the bones Hence the importance of considering the phosphate level before attempting to interpret the observed calcium content in a given patient [1]

The blood serum calcium usually is within normal limits in rickets osteomalacia Paget s disease senile osteoporosis calcinosis universalis and in tetany induced by alkalosis It is elevated in hyperparathyroidism hyperproteinemia and following the administration of excessive doses of vitamin D parathyroid hormone or dihydrotachysterol[6] It is reduced to 4 to 8 5 mgm per 100 c c in hypoparathyroidism hypoproteinemia hyperphosphatemia as in nephritis and uremia in infantile tetany and occasionally in rickets osteomalacia and senile osteoporosis[2]

Phosphorus —The inorganic phosphorus of the blood normally varies from 2 5 to 4 mgm per 100 c c Its level may vary directly or inversely with alterations in the calcium content Thus it usually remains at a normal level despite the increase in calcium observed in multiple myeloma or metastatic carcinoma[8] On the other hand the phosphate level varies inversely with the calcium level in parathyroid disease being increased in hypoparathyroidism and decreased in hyperparathyroidism

The inorganic phosphate of the blood may be markedly increased in renal deficiency the resulting hyperphosphatemia being accompanied by a reduction in the calcium level The status of renal function therefore always must be taken into consideration in evaluating the significance of observed changes in calcium as well as inorganic phosphate levels

At the levels encountered in normal blood the inorganic phosphate is entirely in a diffusible state However, hypercalcemia as produced for example by the

bones The significance of the chemical findings in any case demands careful interpretation and consideration of other related blood constituents and clinical findings as shown in the following discussion Unless this be done one is apt to be misled into grievous errors

TABLE I

CHEMICAL FINDINGS IN THE NORMAL ADULT IN THE MORE COMMON BONE DISEASES

	Blood serum calcium	Inorganic phosphate of blood	Phosphatase activity of blood serum	Calcium Excretion	
				Urinary	Fecal
Paget s disease	Normal	Normal	Very high	Normal	Normal
Multiple myeloma	Frequently high	Normal	Normal or slightly elevated	High	
Osteomalacia	Normal or low	Normal or low	Slightly increased sometimes very high	Low	Low
Metastatic carcinoma of bone	Sometimes high	Normal or low	High in presence of metastasis to liver		
Hyperparathyroidism	High	Low	Increased	Increased	Normal
Senile osteoporosis	Normal or slightly below normal	Normal	Normal	Normal	Normal
Fragilitas ossium	Normal	Normal	Normal or slightly increased	Normal	Normal

Calcium — The calcium of the blood is present almost entirely in the plasma, and hence serum is utilized for determinations clinically of the blood calcium content The normal blood serum calcium varies from 9 to 11 5 mgm per 100 c c In abnormal states values of 12 to 16 usually are encountered although in late stages of hyperparathyroidism values as high as 18 to 20 have been recorded[6]

The serum calcium is present in several forms and an appreciation of this fact aids in understanding the variations observed in disease About 45 to 65 per cent of the total calcium is present in a diffusible state, and this diffusible moiety is almost entirely ionized[9] Moreover this ionized fraction of the calcium, which amounts to 4 75 to 5 25 mgm per 100 cc, is relatively constant, even in many

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injection of parathyroid extract causes a partial conversion of the phosphate to a non diffusible form The significance of this in pathological states has not been determined

Phosphatase — The phosphatase present in normal blood serum is almost entirely of the variety active in alkaline media and is identical with that found in bone[1] Its concentration in blood reflects the content of the enzyme in the bones and the severity of several bone diseases may be correlated roughly with the enzyme content of the blood [4] An increased concentration of serum phosphatase occurs especially in such bone diseases as are attended by the formation of abnormal bone as in Paget s disease or of osteoid tissue, as in rickets [1] Mere bone destruction however is not associated particularly with an increase in the concentration of the enzyme[1]

Normal blood sera of adults contain from 1 5 to 4 0 Bodansky units of alkaline phosphatase per 100 c c and 0 to 0 4 units of the acid phosphatase[6] The latter is formed in the prostate as well as in other organs and is increased in carcinoma of this gland with metastasis This phosphatase is used as a measure of the extent of this metastasis and as an indication of the adequacy of therapy [3,33] In osteitis deformans or osteitis fibrosa cystica, where the alkaline phosphatase values are exceptionally high the acid phosphatase may be moderately increased also

Obstruction of the biliary system produces a retention of phosphatase in the blood This fact may be utilized in the differentiation of hemolytic jaundice, in which the phosphatase is unaffected from the obstructive variety However, it also vitiates the significance of phosphatase determinations in bone diseases in the presence of hepatic disease[7]

An increased alkaline phosphatase of the blood is noted also in tuberculosis of the bone[1], during the last trimester of pregnancy [1] in Hodgkin s disease following invasion of bone and in Boeck s sarcoid[9] In rickets the phosphatase activity may reach values of 20 to 60 units compared to 5 to 15 for the normal child Phosphatase determinations in this disorder reflect more accurately the severity of the disease than do determination of the calcium or phosphorus[1]

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PART II

PAGET'S DISEASE OF BONE
(*Osteitis Deformans*)

By E A LOCKE
REVISED BY ARTHUR GROLLMAN

INTRODUCTION

Definition — A chronic progressive disease of the skeleton usually beginning in middle life which leads to a symmetrical and usually painful thickening and bowing of the long bones as well as hypertrophy and deformity of the skull and other units of the skeleton

Historical — The first description of osteitis deformans was given by Sir James Paget[48] who in 1876 presented to the Medico Chirurgical Society of London a paper entitled On a Form of Chronic Inflammation of Bones (Osteitis Deformans)' He reported five cases and gave so masterly a description of the clinical picture symptoms and sign of the disorder that comparatively little has been added since to our knowledge of the advanced clinical form of the malady In a second paper published in 1882 Paget[49] recorded further observations on these cases and reported seven additional ones Thirteen years after his first communication he stated in a short report[50] that he had observed a total of twenty three cases

In his original paper Paget describes the disease as follows It begins in middle age or later is very slow in progress may continue for many years without influence on the general health and may give no other trouble than those which are due to the changes of shape size and direction of the diseased bones Even when the skull is hugely thickened and all its bones exceedingly altered in structure the mind remains unaffected

' The disease affects most frequently the long bones of the lower extremities and the skull and is usually symmetrical The bones enlarge and soften and those bearing weight yield and become unnaturally curved and misshapen The spine whether by yielding to the weight of the overgrown skull or by change in its own structures may sink and seem to shorten with greatly increased dorsal

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Historical — The first description of osteitis deformans was given by Sir James Paget[18] who in 1876 presented to the Medico Chirurgical Society of London a paper entitled On a Form of Chronic Inflammation of Bones (Osteitis Deformans) He reported five cases and gave so masterly a description of the clinical picture symptoms and signs of the disorder that comparatively little has been added since to our knowledge of the advanced clinical form of the malady In a second paper published in 1882 Paget[19] recorded further observations on these cases and reported seven additional ones Thirteen years after his first communication he stated in a short report that he had observed a total of twenty three cases

In his original paper Paget describes the disease as follows It begins in middle age or later is very slow in progress may continue for many years without influence on the general health and may give no other trouble than those which are due to the changes of shape size and direction of the diseased bones Even when the skull is hugely thickened and all its bones exceedingly altered in structure the mind remains unaffected

The disease affects most frequently the long bones of the lower extremities and the skull and is usually symmetrical The bones enlarge and soften and those bearing weight yield and become unnaturally curved and misshapen The spine whether by yielding to the weight of the overgrown skull or by change in its own structures may sink and seem to shorten with greatly increased dorsal

and lumbar curves the pelvis may become wide the necks of the femora may become nearly horizontal but the limbs, however misshapen, remain strong and fit to support the trunk

"In its earlier periods and sometimes through all its course, the disease is attended with pains in the affected bones, pains widely various in severity and variously described as rheumatic gouty or neuralgic not especially nocturnal or periodical It is not attended with fever No characteristic conditions of urine or faeces have been found in it It is not associated with syphilis or any other known constitutional disease unless it be cancer"

Medical literature previous to 1876 contains reports of cases which may be examples of osteitis deformans but the description of the conditions is so meager as to make the diagnosis very doubtful As early as 1801 Saucerotte [6] described the case of a man who died at forty and whose bones generally were enlarged A similar instance of hypertrophy of nearly the whole skeleton in a man who died at seventy was published by Rullier in 1809 From the meager description given Paget considers these cases as doubtful Wrany [4] in 1867 recorded a case of a woman of fifty with spongy hypertrophy of the cranium, atrophy of the face spongy hypertrophy of the spine pelvis and left lower leg with elongation' He summarizes the process as a 'rarefying osteitis with softening' Paget regarded this case as probably a true example of osteitis deformans The only undoubted example of the disease described prior to Paget was published by Wilks[7] in 1869 It is the same as Case 4 of Paget s series

The status of Paget s disease of bone remained in a rather confused state during the next half century This was due to a failure to differentiate it from osteitis fibrosa cystica Von Recklinghausen[53] himself who described the latter disease, considered Paget s disease to be only a modified form of osteitis fibrosa cystica although he differentiated the two histologically Other German pathologists followed von Recklinghausen and as late as 1923 described osteitis deformans and osteitis fibrosa as the hyperostotic and hypostotic forms respectively, of fibrous osteodystrophy This state of confusion was dispelled finally by the demonstration of the etiological relationship of hyperparathyroidism to generalized osteitis fibrosa cystica and the establishment of definite diagnostic criteria for the recognition of Paget s disease [6]

Synonyms —A considerable array of formidable names, for the most part in accordance with the author s conception of the pathology of the disease have been applied to this condition A list of the most common of these terms is as follows osteitis deformans (Paget) Paget s disease osteomyelitis fibrosa (v Recklinghausen) osteomalacie locale (D Ollier) sclerose osseuse hypertrophique (Menetrier and Gauckler) osteomalacia chronica deformans hypertrophica (Schmieden) osteitis ossifiante diffuse (Lancereaux) megalo osteomyelitis fibrosa

(Ganiciero) osteolyose (Lobstein) pongiose Knochenhypertrophie Cranio sclerosis (Huschke), osteomalacie hypertrophique benigne (Vincent) hyperos tose generalisee osteite condensante (Volkmann) pseudo rachitisme senile (Pozzi) rhumatisme osteo hypertrophique des diaphyses et des os plats (Fereol) diffuse hyperostosis The disease usually is designated as osteitis deformans but is most appropriately referred to as Paget s disease of bone since it is only in its late stages with the involvement of many bones that deformity occurs

INCIDENCE

Osteitis deformans in its clinically recognizable form is a rare disease and only a small number of cases have been reported since Paget s first publication Hur witz [3] found only three cases among 30 000 medical admissions to the Johns Hopkins Hospital and Da Costa[1] the same number in 38 000 admissions to the Jefferson Hospital Philadelphia Cutler[11] encountered only 7 cases from 285 000 outpatients observed at the Massachusetts General Hospital during a period of twelve years while *Carman and Garrick*[8] *found 15 cases among 237 000 admis* sions to the Mayo Clinic Gutman and Kasabach collected records of 104 cases diagnosed at the Presbyterian Ho pital New York among 200 000 patients seen from 1905 to 1935 By 1914 only 213 cases had been described and only about 500 cases of the disseminated form of the disease have been reported by now The disease is however, not as rare as these figures would indicate The subjec tive symptoms rarely are prominent or severe and in consequence the patient very seldom enters a hospital and comes to the physician s attention only when suffer ing from some other malady In the majority of cases the typical changes in the bones are revealed by x ray examination of the skeleton when not otherwi e sus pected

Pathological examination of the skeleton reveals Paget s disease with much greater frequency than does clinical experience Thus Schmorl [7] by careful mi croscopic examination of the skeleton found 138 cases of the disease in 4 614 autopsies on persons past 40 years of age The disease in this age group thus has an incidence of 3 per cent when sought for by systematic pathological examina tion This high incidence at autopsy is due to the fact that the disease frequently is limited to the lumbar vertebrae the sacrum or bones of the pelvis without in volving the extremities and without leading to any clinical manifestations during life

Paget s disease has been demonstrated in archeological specimens[4] and in the skeleton of American Indians It has been observed in the Japanese and in the Negro There appears to be no particular geographic or racial distribution of the disorder

Hypertrophic lesions have been described in monkeys, which have been considered as Paget s disease and which show a gross resemblance to the disease as observed in the human However, the identity of the condition in the two species is questionable

Age

Osteitis deformans is a disease of advanced life In a majority of cases the disease begins before the fiftieth and only rarely as early as the thirtieth year As a rule however the patient does not consult a physician until many years later Several instances of the disease at ages varying from 12 to 17 years are often quoted but a careful reading of the original reports does not convince one that they are genuine cases of Paget s disease Moizard and Bourges[4] report one instance with symptoms first noted at 21 which seems to be a true example of osteitis deformans Stilling[6] records a case which was first seen at age 92 The 67 cases of Packard Steele and Kirkbride[47] gave an average age of onset as 49 5 years and an average age when first coming under observation, as 61 years The 48 cases observed by Locke averaged 45 5 years at time of onset and 57 years at time of coming under observation

The distribution as regards age is shown in the following table of Gutman and Kasabach based on 116 cases

Age group in years	25–29	30–39	40–49	50–59	60–69	70–79
Number diagnosed	1	6	22	34	40	13
Onset of symptoms (27 cases asymptomatic)	2	9	29	35	12	2

It must be remembered that the disease may be present for a number of years before any symptoms are noted Schmorl [7] however failed to observe any pathological changes of Paget s disease even in its mildest form in a person under 40 years of age A definite etiological importance thus must be attached to age and this must be taken into account in entertaining the diagnosis in a given patient

Sex and Occupation

Males are perhaps more commonly afflicted Packard Steele and Kirkbride s[4] series showed 65 per cent Locke s series 58 per cent males In the 138 cases of the disease observed by Schmorl [5] males also constituted 58 per cent In Gutman and Kasabach s 116 cases however the distribution as regards sex was equal There is no correlation between the incidence of the disease and the race, occupation or station in life of the patient

Etiology

The cause of the disease is unknown Numerous theories variously based on clinical histological chemical and bacteriological characteristics of the disorder have been advanced from time to time to explain its pathogenesis but none of these does so satisfactorily The older views according to which the disease represents an unusual manifestation of gout rheumatism bacterial infection trauma syphilis or nervous dystrophy have been thoroughly discredited and need no further comment Various endocrine organs have been implicated in its etiology but this view rests on no sound evidence Moehlig and Adler[41] have stressed the frequency of disturbances in carbohydrate metabolism in Paget s disease and postulate that the pituitary is involved in this disease as well as in osteoporosis However there is no convincing evidence to support this hypothesis

Malignancy —The frequent association of osteitis deformans and malignant tumors is unquestioned Paget states that of 8 cases who were traced to the end of life 5 developed either cancer or sarcoma and on the basis of this experience takes the stand that the intimate relation between osteitis deformans and malignant tumors is decisive Of the 14 of Locke s cases who died while under observation 3 showed this complication Packard Steele and Kirkbride[47] found cancer in 4½ per cent and sarcoma in 7½ per cent Bird found 7 of 64 cases complicated by bone sarcoma an incidence of 9 per cent Speiser[61] observed sarcomatous degeneration in 4 per cent of his series of 150 cases Breslich' collected 22 instances of sarcoma involving bones affected by Paget s disease Of 71 cases of osteogenic sarcoma in patients over 50 years of age Coley and Sharp[13] found 28 per cent to be associated with sarcoma

There are several points of interest in connection with the problem of the association of sarcoma and Paget s disease When the two are associated the bones involved by the neoplasm usually are those associated with Paget s disease The sarcomatous foci often are widely disseminated with multiple foci in the bones involved by Paget s disease The histological picture of the osteogenic sarcoma also differs from that usually seen in sarcoma uncomplicated by Paget s disease The chief difference between the tumor and the fibrous tissue between the trabeculae is the unrestrained growth of the former [9] The intercellular material may be scant and the calcification usually observed in osteogenic sarcoma may be absent in Paget s disease complicated by this tumor

There would thus appear to be an important causal relationship between polyostotic Paget s disease and the osteogenic sarcoma which so frequently complicates its course In this respect Paget s disease differs from the other dystrophic bone diseases The great proliferative capacity of the connective tissue in Paget s disease endows it with the potentiality for malignant change It would be errone

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The initial process in Paget s disease is a resorption of bone which in turn is followed by a secondary fibrous proliferation in the bone marrow This reactive process as we have seen may lead in some cases to malignant metaplasia Jaffe[8] has suggested that the initial resorption of bone may be induced by the changes of senile bone atrophy

This view is supported by the presence in Paget s disease of areas of simple smooth atrophy According to this view Paget s disease represents a compensatory reaction of the osteogenic marrow connective tissue to the normal smooth resorption characteristic of senile bone atrophy According to this view it is a failure of the normal replacement process to which the bones are subject that results in the pathological picture observed in Paget s disease[1]

Pathology

The pathology of this disease is concerned primarily with the osseous system A wide variation in the character and degree of the bone changes is observed depending on the duration and extent of development of the process Of whatever stage however the fundamental changes are unusually definite and constant

It is only in its late stages when marked deformity has occurred that Paget s disease gives rise to symptoms Hence the older concepts of the pathology of the disease based as they were on clinical observation alone have had to be modified on the basis of more recent roentgenological and anatomical studies The older view that the bones most commonly affected are the skull and long bones of the legs and arms is no longer tenable It is true that when the disease becomes manifest to the patient it is due to involvement of these bones but an analysis of 138 cases studied carefully at autopsy by Schmorl[17] showed the frequency of the disease in single skeletal parts to be as follows

Sacrum	56 5 per cent
Spine	50 0
Right femur	31 2
Skull	28 3
Sternum	23 2
Pelvis	21 7
Left femur	15 2
Clavicle	13 2
Tibia	8 0
Ribs	7 2
Humerus	4 3

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Heredity — Several cases of the disease have occurred in the same family, indicating the possible existence of an inherited predisposition to the disorder In the 213 cases collected by Da Costa, Funk Bergeim and Hawk[1] there were 15 instances with positive family history or 7 per cent In 7 there were 2 cases in the same generation and in 2 2 or more cases in two generations A definite positive family history was obtained by Locke in 10 of his 48 cases Five cases were in two members of the same generation and 5 in parent and child One of the latter group gave a typical history of the disease in both his father and paternal grandfather Three members in one family were observed by Moehlig and Adler[41] In Gutman and Kasabach s 116 cases 3 siblings and their mother were affected in one case 2 brothers and a son in another and a brother and sister in a third instance Such figures cannot fail of significance, though how far heredity is a determining factor in causing the disease c innot be stated

Arteriosclerosis and Senile Degenerative Changes — The atheromatous theory of osteitis deformans has received much attention throughout the literature of the subject More or less generalized arteriosclerosis usually of a striking type has been observed so commonly in these cases that it may almost be regarded as a universal concomitant of the disease That atheromatous alterations in the arteries may lead to nutritive changes in osseous tissue is well recognized and naturally has led to the supposition that the arteriosclerosis associated with osteitis deformans is responsible for the observed changes in the bones According to this view the bone changes are due to extreme sclerosis of the nutrient arteries of the affected bones

However the process in the bones associated with such vascular changes in a main trunk artery or the nutrient vessel are as a rule essentially those of atrophy and quite unlike that seen in Paget s disease Moreover it is difficult to explain why if osteitis is due to arteriosclerosis the lisease does not occur much more commonly considering the great frequency of the former condition at the period of life when osteitis most commonly develops The lesions of Paget s disease are seen rarely in the hands or feet, which are generally affected in occlusion of the peripheral vessels

The Possible Nature of Paget s Disease — In arriving at any conclusion as to the possible nature of Paget s disease several facts must be kept in mind The fact that the disease frequently is limited for a long time to a part of a single bone would indicate that we are not dealing with a generalized systemic disease due to some metabolic or endocrine disturbance such as is observed in osteomalacia or generalized osteitis fibrosa cystica Although the latter conditions may affect certain areas of the skeleton more prominently than others, the lesions are gen

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It is evident from the above tabulation that the bones most commonly affected are those subjected to weight bearing the pelvis, spine and right femur The skull however, is an exception to this generalization as is also the fact that the mandible and maxilla which are subject to considerable strain, are affected only infrequently On the other hand when the disease affects the spine, the lumbar vertebrae are affected almost twice as frequently as the thoracic and almost four times as often as the cervical vertebrae In only 4 instances in a total of 69 cases in which the vertebral column was involved did the disorder affect the entire spine In most cases only one to four vertebrae were affected

Although many bones may be affected, it is erroneous to refer to the disease in these cases as generalized osteitis deformans for this term implies a systemic disorder Instead the term polyostotic as first suggested by Pick is to be preferred Where only one bone is affected the condition is denoted as monostotic, and where only a portion of the bone is involved, as merostotic (from the Gr μερος a part) It is the polyostotic or disseminated form of the disease that constitutes the clinical entity described by Paget The bone changes in the monostotic or merostotic types of the disease which usually involve the pelvic, sacral and vertebral bones are similar to those observed in the polyostotic variety but since they give rise to no deformity are devoid of clinical signs or symptoms except perhaps for a history of pain [4] In the earliest stages of the disease small foci consisting of thickened trabeculae without involvement of the intertrabecular marrow may be present These foci may be so small as to be invisible to the unaided eye and require histological examination for establishing the diagnosis of Paget s disease

The disease almost invariably shows a bilateral but very asymmetrical and irregular involvement However unique exceptions to this rule may occur as in the case of Klippel and Weil[3] in which the disease was strictly confined to the right side of the skeleton or the case cited by Schmorl[3] in which only half of the skull was involved

The gross changes (Figs 1 and 2) consist primarily in a general thickening and in the case of the long bones of a conspicuous bowing both characteristics being in evidence throughout the shaft and in advanced stages involving the epiphysis as well Not infrequently the bone is increased to twice its normal size In all cases the bowing is in the nature of an accentuation of the normal curve together with a moderate degree of torsion Actual lengthening also takes place The normal ridges and prominences may be the first to show the hypertrophy As the disease progresses the normal markings of the bone are gradually lost The diseased bone appears plump and misshapen and has been likened in outer appearance to roughly hewn stone The general outline is fairly regular but the surface is extremely uneven Occasionally the even outline is broken by rather

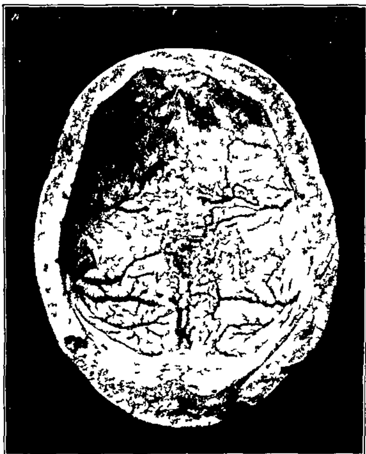


FIG 1 —Paget s disease of the bone (osteitis deformans) calvarium from male ag 63 Note the great thickening porous texture roughened surface and deepening of the grooves for vessels

Facing 4 8

large osteophytic outgrowths Such proliferation in a few instances may take the form of typical Heberden s nodes These outer modifications are particularly common to the tibia femur fibula humerus radius and ulna Paget[14] described the general appearances of the long bones as follows The outer surface of the walls of the bones was irregularly and finely nodular as with external deposits or outgrowths of bone deeply grooved with channels for the larger periosteal blood vessels finely but visibly perforated in every part for transmission of the enlarged small vessels Everything seemed to indicate a greatly increased quantity of blood in the ves els of the bone

The gross appearance just described is brought about by the removal of the normal bony structure and its replacement by excessive amounts of new bone which is deposited in a coral like or spongy form This characteristic spongy ap pearance is due to the thick trabeculae arranged irregularly with projecting tooth like surfaces In the case of the long tubular bones this abnormal appearance is less striking since these bones normally contain trabeculae of variable thickness at their spongy ends The disease in the long tubular bones begins in the spongi osa of the ends and progresses toward the middle of the diaphysis The compacta undergoes gradual thickening with the assumption of a lamellated appearance [6]

The periosteum is deeply injected in many places and moderately adherent Freund[15] has demonstrated that periosteal activity is responsible for the increased thickness of the tubular bones observed in Paget s disease The new bone prolif erated by the periosteum rapidly becomes affected by the disease process and thus is obscured Parosteal tissue also participates in the periosteal new bone forma tion Periosteal activity usually is very evident in bones which have been frac tured [6]

The medullary cavity of the diseased tubular bones varies in its appearance but usually is widened with an open arrangement of trabeculae with irregular spaces between them In some cases the marrow cavity may be elongated but contracted This cavity may extend to the articular ends of the bone and displace the articular end plate There may be fat filled cavities enclosed by thickened trabeculae which in the x ray give the appearance of cysts The marrow cavity may be entirely obliterated by fine spongy bone This so called endosteal form of Paget s disease is rare and doubt has been expressed as to the cases so described being true examples of Paget s disease

The changes in the skull (Fig 1) are among the most striking observed in the skeleton The whole calvarium is uniformly enlarged often to an extraordinary degree but the degree of thickening may be irregular and is most marked in the occipital regions The skull may increase to as much as 60 to 66 cm in circum ference as compared with a normal of 54 to 58 cm One of Paget s cases measured 71 cm The outer surface is fairly regular and symmetrical but with special

prominence in the occipital parietal and frontal regions The sutures often are obscured Frequently the mastoid processes of the temporal bones and the malar bones are prominent In a few cases the bones of the face and especially the lower jaw show considerable hypertrophy, although as a rule these bones remain unchanged The skull cap cuts easily due to its soft and friable nature All normal structural markings may be absent As in the case of the long bones the tissue is rich in blood soft and augmented in thickness Areas suggesting hemorrhagic infarction may be found Islands of varying size of dense homogeneous bone are present occasionally These islets of ivory bone are demarcated in such a way as to suggest that they might eventually become sequestrums[33] The frontal sinuses may be obstructed or entirely obliterated by new bone The inner surface of the calvarium is more irregular and dense than the outer and is often closely adherent to the dura The grooves for vessels are deep and the orifices voluminous Although the base of the skull may appear normal in some advanced cases, it usually shares in the alterations affecting the calvarium As a result of the osseous hypertrophy there may be some narrowing of the foramina which give passage to vessels and nerves including the foramen ovale The vascular foramina in some cases may become enlarged

The spine as already indicated is the most frequent site of involvement It is only in advanced cases with involvement of several vertebrae that changes in the spine become evident clinically The spine may be rigid throughout due to extensive ankylosis with a very pronounced kyphosis involving especially the thoracic portion Scoliosis of slight degree may occur also Grossly the vertebrae give a characteristic spongy appearance The disease may, in its early stages, involve only the body of the vertebrae but ultimately spreads to include the processes as well Deformation of the diseased vertebrae results, and when several contiguous vertebrae are involved the disease process may extend through the intervertebral disc with fusion of the vertebrae

The tibia when involved becomes thick and curved (Fig 2) but may become atrophic in cases of enforced inactivity of the extremity for example following fracture The fibula is involved rarely and remains straight despite the marked bowing of the tibia The short tubular bones are also usually exempt from the disease and the facial bones are involved only rarely The entire sternum may be involved but most often only the manubrium The ribs are affected in polyostotic cases sometimes with enlargement of the costal cartilages near the costochondral junction The clavicles may be involved diffusely or only at their extremities The scapula when affected usually is only slightly involved Only in severe cases is the pelvis diffusely involved with deformity similar to that seen in osteomalacia Most often only a part of one or more of the innominate bones is diseased[37]

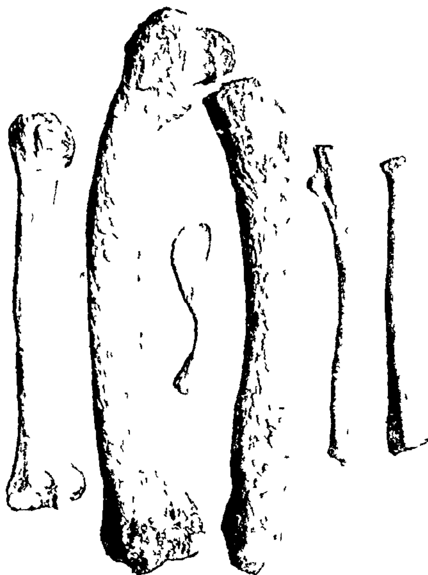


FIG —Paget s disease of the bone (osteitis deformans) male age 63 humerus femur clavicle tibia ulna and radius Observe the enormous thickening throughou the cylindrical form the spongy character roughened surface and accentuation of the normal curves

Facing 430

The joint structures are seldom involved except late in the course of the disea e when limitation of motion and slight pain may result from the deformity at the articular ends of the bones Those most affected are the knees hip ankle, shoulder and elbow Actual arthritis has been reported but probably has no direct connection with the osteitis On the other hand the severe changes in the articular cartilages as reported by Freund [5] were not typical of that observed in arthritis deformans They were marked by exostoses which microscopically resemble the bone of Paget s disease

Next to the osseous changes the most constant pathological finding in Paget s disease is arteriosclerosis In advanced cases of the disease cardiovascular changes of an outspoken type are found so constantly that they have been regarded not as a complication but as an essential part of the disease The extreme degree of atheroma of the arteries met with in this disease is seldom seen except in extreme old age myxedema or diabetes So marked is the calcification in the arteries that in many of the cases the arteries of the arms and legs stand out in the x rays as dense tortuous shadows A majority of the cases toward the end of life develop striking clinical evidences of arteriosclerosis and common causes of death are cerebral thrombosis and cardiac failure Valvular lesions due to sclerosis are common late in the course of the disease and at post mortem general cardioarterial sclerotic changes have been found almost constantly However in view of the advanced age of the patients and the frequency of arteriosclerosis in the senile it is doubtful if the vascular changes are es ential characteristics of the disease or that they play any part in its pathogenesis

Microscopic Anatomy

Histologically Paget s disease presents a characteristic appearance with certain peculiarities which are distinctive and distinguish it from other affections of bone

Butlin[4] (see Paget[18]) who made the pathological studies on Paget s first cases described the microscopical appearances He observed that the Haversian systems and canals were much diminished in number but enormously widened and that many were confluent the communicating spaces being filled with blood vessels and ill developed tissue The sides of these canals were not smooth but eaten out to form the Howship s lacunae so characteristic of inflammation New and incompletely developed bone was very evident beneath the periosteum Fibrous tissue and fibrocells were abundant The evident absorption of the original bone as well as its manner of absorption led Butlin to consider the process as a true chronic inflammation but subsequent studies have shown the error of this view

The more recent work of Schmorl [7], Knaggs[31], Freund[1], Jaffe [6] and others have demonstrated the histological characteristics of the disease The striking histological feature in an advanced case of Paget s disease is the mosaic structure of the involved bone Variously sized irregular fields of lamellar bone are separated by the so called cement lines which stand out deeply colored in preparations stained with hemotoxylin after fixation in formalin and decalcification This mosaic structure has been aptly described by Knaggs[31] as if the bone were decorated with internal curvilinear markings There is no tendency for the fragments comprising the mosaic to be arranged about the vessels to form Haversian systems[1] as in the normal The mosaic is only present in areas of the bone in which the disease is completely developed and is not found in the connective tissue bone which replaces the marrow

The mosaic structure just described originates as a result of the alternate resorption and deposition of bone which characterizes Paget s disease The resorbed areas in which new bone is not deposited remain as the cement lines If resorption is progressive no mosaic structure results fine fibered connective tissue bone appearing in the vascular fibrous tissue which replaces the original bone Jaffe Bodansky and Chandler by inducing simultaneously rapid absorption (by injections of parathyroid hormone) and deposition (by high calcium diets containing elemental phosphorus) of bone were able to induce an irregular mosaic suggestive of that observed in Paget s disease experimentally The lesions thus induced were not however typical of that encountered in the human, as indeed was not to be anticipated

In the cortical areas of the bone the disease appears to start in the Haversian canals progressing to the periosteal and endosteal surfaces The first changes noted are the appearance of osteoclasts in Howship s lacunae in some of the vessel canals The canals enlarge as more osteoclasts and blood vessels appear Adjacent canals fuse and the marrow spaces become filled with a spindle cell connective tissue in which in turn new bone is deposited Osteoblasts line the surfaces of this newly formed bone When the entire cortex has been transformed periosteal proliferation and resorption on the medullary surface begin The newly formed periosteal bone is reddish in color due to its high degree of vascularity and is transformed in turn into Paget s bone

The marrow in the long tubular bones becomes fatty and hemorrhagic Necrosis of large areas of intertrabecular marrow may occur with the ultimate production of cystic spaces

There is a natural tendency for Paget s disease to undergo spontaneous healing and one may encounter areas in which the reparative process is evident The irregular cement lines may however persist for years in these healing lesions During the healing process the bones tend to become sclerotic [6] In patients,

who have been bedridden for some time before death marked osteoporosis occurs as in normal bone [7]

Biochemical Considerations

Composition of the Bones — The organic matter of the bones affected by Paget's disease is increased in amount the calcium and magnesium content decreased while the total chlorine phosphorus and sulfur content remains essentially normal Inasmuch as the severity of the disease varies and separative processes frequently are in progress no constancy in the composition of the bones is noted The amount of fat in the bones also is irregular but usually is greatly increased Analyses by Smith and Emerson showed a CaO content of 25 to 42 per cent MgO 0 14 to 0 68 per cent organic matter 42 to 49 per cent compared to 47 4 0 8 and 37 8 per cent respectively for normal bone

Metabolic Functions — Studies on the mineral metabolism in Paget's disease have yielded divergent results Several authors[1, 3] report a positive calcium magnesium and phosphorus balance Sulfur on the other hand shows a negative balance The significance of these findings in the case of sulfur is unknown but the positive balance in the case of calcium phosphorus and magnesium is undoubtedly a reflection of the deposition of these elements in newly formed Paget's bone It must be remembered that although the bones in this disease may be deficient in minerals their actual size is increased so that the total amount of mineral salt actually may be increased over the normal Snapper[6] observed a normal calcium excretion in seven cases of Paget's disease as compared to controls under the same dietary conditions Sugarbaker[6] on the other hand found a negative calcium and phosphorus balance generally to be present during the earliest and more active stages of the disease There is thus a striking inconsistency in the findings as regards the metabolism of calcium and phosphorus in the disease This is not entirely unexpected when one considers the natural remissions and exacerbations and the intermittent osteoclastic and osteoblastic activities which characterizes the disease

London and Bernheim[17] administered calcium gluconate intravenously in 17 patients suffering from Paget's disease and observed an increased calcium tolerance indicating an increased affinity of the bones and tissues for calcium in this disease

The chemical findings in the blood are discussed under Differential Diagnosis

Symptoms

The onset invariably is insidious the progress of the disease being so gradual that the patient is scarcely ever conscious of its presence until many years have

passed Very commonly his first knowledge of his deformity is the result of his attention being drawn to it by his friends or family Even in the advanced stages of the disease the patient may not have observed the striking changes in the skeleton In the great majority of cases the first symptom is pain, usually in the skin At the same time it may be discovered for the first time that the leg is becoming bowed Even when the deformity is marked and general symptoms have developed the condition often is regarded merely as the infirmities of old age Except in those cases suffering from pain the victims of the disease do not seek medical advice until very late in its course In hospital practice the disease is almost invariably discovered fortuitously by x ray in a patient under treatment for some entirely independent condition

Pain usually is the first and frequently the most prominent symptom of the disease It is located most commonly in the lower legs and especially over the front of one or both tibiae and is described as a dull, "rheumatic type felt deep in the bones The pain is seldom constant and presents all possible grades from mere discomfort to actual paroxysms of a lancinating character It is worse at the end of the day or at night and especially after long standing and unusual fatigue as in walking The patient finds it difficult to get the leg in a comfortable position A prone position often affords relief suggesting that hyperemia may be an important factor in causing it Much more rarely and only late in the disease the same type of pain may be felt in the thighs pelvis spine and arms Pains in the skull are rare An intense burning and feeling of increased local temperature often accompanies the pain Elting[13] suggests that the pain is possibly the result of distention of the periosteum Both the pain and the burning are most intense in the early stages of the disease and gradually subside after a varying number of years A few cases are recorded where pain was absent throughout the course of the disease or appeared as a very late symptom

Apart from pain symptoms during the early years of the disease are not prominent Osteitis is often seen in those of apparently robust health and it may be only after a long period of ten to fifteen years following the onset of pain that the patient feels any limitations from the process in the bones Sooner or later however, in a majority of instances the patient finds that he becomes easily fatigued and notes a stiffness and clumsiness in moving about Getting up from a sitting or prone position is difficult Muscular weakness likewise is common When first seen the patient often presents a striking picture of premature senility In the late stages of the disease cardiovascular symptoms are in the foreground and frequently first lead the patient to seek medical advice Vertigo, palpitation and dyspnea are among the most common subjective symptoms Actual cardiac decompensation with edema is not unusual Extreme arteriosclerosis of the peripheral vessels is found almost constantly in the late stages of the disease

One of the most constant and severe symptoms is cramps in the muscles of the lower legs They almost invariably appear soon after the patient goes to bed Headache is also a very common symptom

A history of failing vision is obtained in about half of the cases due perhaps to the effect of the marked alterations taking place in the base of the skull Paget records that of his twenty three cases four became totally blind one had choroiditis and three had retinal hemorrhages

Gradual impairment of hearing is the rule and total deafness often results [7] Apart from the influence of arteriosclerosis the cause is probably to be found in the compression of the labyrinth by the hypertrophy of the base of the skull as suggested by von Kutscha[39]

It is surprising that despite the marked changes observed in the cranium[40] and the spine psychic and neurological symptoms are not prominent the occasional memory weakness and confusion observed being only those incident to old age Headache paresthesia and vertigo are not uncommon however Occasionally psychoses and neurological symptoms may occur [16, 17, 1, 39, 44, 75]

The muscles of the legs or arms if the bone is affected show atrophy and occasionally edema Tenderness to pressure over the muscles may be present The skin of the lower legs undergoes marked alterations It is thin often irregularly and deeply pigmented and sometimes with ulcerations or atrophic changes resembling cicatrices In those cases with great enlargement of the calvarium the hair is thin or more often wanting The sensations and reflexes are normal

Since the disease is essentially confined to the skeleton it is natural that the objective signs should be the most prominent As the disease progresses the deformities become more and more pronounced and in its most advanced form afford an extraordinary picture (Fig 3)

In the classical fully developed case the head appears enormous (Fig 3) but on close examination the enlargement is found to be largely if not wholly confined to the calvarium It is symmetrical but with a tendency to irregularities of the surface Especial hypertrophy of the supraorbital portion of the frontal bone and the malar processes gives to the skull a very massive appearance The head looks too large for the body The neck is short and the head seems to rest directly on the shoulders In its most developed cases the enormous head is thrown forward with the chin nearly touching the sternum Motion of the head is greatly limited and the chin can be raised only slightly from the chest In contrast the face is small In a few cases the bones of the lower jaw were moderately hypertrophied The marked broadening of the frontal portion of the skull gives to the face a distinct triangular outline A large majority of the males give a definite history of having year by year been obliged to increase the size of their hats and not a few have found it necessary to have their hats made to order

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Fig 3 —Paget s di ease of the bone (osteitis deformans) male age 60

The trunk in comparison with the head and prominent limbs often appears small The thorax is compressed laterally and has a variable quadrilateral shape Immense increase of the anterior posterior diameter accompanies the decrease in the lateral The whole thorax is rigid and in consequence the respiration is mainly diaphragmatic in type Hypertrophy of the ribs takes place only late in the course of the disease The clavicles are among the bones earliest involved and are greatly thickened and misshapen Less constantly the scapulae may show similar changes These modifications give to the entire shoulder girdle a striking prominence The whole spine becomes bowed with the most marked curve in the thoracic portion and finally develops complete rigidity Scoliosis is rare

The bones of the upper extremities seldom show very noticeable alterations Most commonly the forearm is curved in its lower half due to bowing of the ulna the convexity being outward and backward when the hand is in the position of supination Pronation usually is complete but supination is much restricted Anterior bowing with thickening of the humerus is less frequent In these bones the x ray very often may show only a third or half of the shaft to be involved

As a result of the anterior curve of the spine and the flexion of the trunk on the thighs the abdomen is greatly contracted from above downward The costal border of the thorax may actually rest on the crests of the ilia The abdomen is small protruding and marked transversely at the level of the navel by a deep groove

The changes in the pelvis are among the most noticeable in the entire body It is very broad and massive with abnormal flaring of the iliac crests The general shape conforms more or less to the female type Due to softening of the bones the heads of the femora may be pushed up into the pelvis

The earliest most constant and with few exceptions the most pronounced deformities are to be found in the legs If confined to the tibia and fibula the bowing is confined to the lower leg When as so happens the femur is affected also the curve embraces the entire leg from the hip to the ankle Its type is always the same namely a broad curve with the convexity chiefly forward No other condition except rickets in children ever gives such an extreme degree of curvature of the legs So great may the bowing become that the legs are crossed, and walking is possible only by a curious awkward motion of extreme torsion of the body and tilting of the pelvis with each step in order that the advancing leg may clear the other When lying down or sitting the legs often are crossed like a pair of open scissors

On standing the knees and ankles are considerably flexed and the feet held somewhat apart strongly everted and one in advance of the other The eversion accentuates the bowing to such an extent that the inner condyles may be widely separated The lower legs present a most distinct and characteristic deformity,

the most striking feature of which is the even broad forward and slightly outward curve *from the knees to the ankles The tibia has lost all its normal markings* and is cylindrical in shape Except for small irregularities the surface is generally smooth It is in this portion of the body that the kin shows the marked changes mentioned earlier

The deformities above mentioned give to the sufferer from osteitis deformans a posture which is peculiar and in advanced stages extremely grotesque The enormous head which is carried forward with the chin nearly touching the sternum the strong kyphosis of the spine the deformed thorax the flexion at the *hip knee and ankle joints produce the peculiar appearance which Paget likened* to that of an anthropoid ape The gait is strangely labored slow and waddling

X Ray Findings

X ray examination (Fig 4) is of the utmost importance not only as essential in showing the type of bone changes but more especially because it is the only means by which the extent to which the skeleton is invaded by the disease can *be determined The roentgenogram* also *permits the detection of the disease be*fore it becomes clinically obvious and also reveals monostotic forms of the disorder when the disea e process is confined to a single bone At this stage of the disease the x ray may reveal involvement of only one side of the pelvis instead of the symmetrical involvement seen in the fully developed disease

Circumscribed areas of osteoporosis may be the first evidence of Paget s disease in the skull These porotic areas subsequently are replaced by an osteosclerotic appearance and the characteristic cotton wool appearance This is seen most frequently in the frontal and frontoparietal areas Areas of osteoporosis circumscripta of the skull may appear in association with the typical cotton wool appearan e of Paget s disease

In addition to the even bowing of the long bones the x ray in Paget s disease reveals coarse trabeculations extending into the shaft or involving the entire bone and replacing the normal fine markings of the cancellous ends of the bones The periosteum may show superficial defects and is fairly uniform in outline except for extreme variations in the amount of lime salts deposited near it Newly formed subperiosteal bone is not seen Extensively diseased bones reveal a feathery or mossy texture cotton wool appearance and are more transparent than normal In later stages areas of new bone tend to become sclerosed[4] and less permeable to the x rays[4]

The x ray appearance in Paget s disease often bears a close resemblance to that seen in metastatic cancer of bone The latter however causes no expansion *of the bony contours and the coarse striations characteristic of Paget s* bone are



FIG 4—Paget s disease of the bone (osteitis deformans) male age 63 X rays of fibula tibia and femur Note the uneven surface enlargement exaggerated curves and double process of rarefaction and sclerosis

Facing 437

complications but are not so frequently present as would be expected considering the deformity of the thorax

Course and Progress

One of the most characteristic features of the disease is its chronicity With very few exceptions the process in the bones is steadily progressive leading to greater and greater deformity with the result that the victim sooner or later becomes in the strict sense a cripple In a few instances where the legs have been crossed and the muscular wasting was extreme the patient has for many years been confined to bed General disability usually goes hand in hand with the growth of the deformity yet it would appear that the osteitis does not materially shorten life Indeed it is very noticeable in reviewing the statistics of the disease that the majority live to old age death often occurring only after the sixth and sometimes the seventh decade The exact duration of the disease is difficult to determine since the onset is so indefinite A course of twenty to thirty years is not rare

An occasional exception is found to the usual progressive course of the disease when the process after a period of years seems to become quiescent the subsequent years of life showing no evidence of increase in the deformity The possibility of such a quiescent stage in the course of osteitis has been proved by repeated x rays of the skeleton over a period of many years Very rarely the disease may come to a standstill and then after some years again becomes active It is probable that a very exceptional case may undergo spontaneous and permanent cure

The osteitis is never the direct cause of death Among the complications leading to a fatal termination cardiovascular disease with or without associated renal trouble is undoubtedly the most common Next in importance is malignant disease bone sarcoma being the most conspicuous Less common terminal affections are pneumonia emphysema and bronchitis pulmonary tuberculosis and apoplexy A few cases have died without evidence of a terminal complication and it has seemed reasonable to attribute death to a fatal cachexia

Differential Diagnosis

With the possible exception of the rare case of osteitis of a single bone or the unusual borderline case diagnosis is never difficult The age characteristic history typical and unique type of deformities and the constant and peculiar x ray appearances described above combine to form a definite picture which can hardly be confused with any other disease of the skeleton

not observed in cancer The skull in metastatic cancer does not show the "cotton wool" lesions of Paget's disease

COMPLICATIONS

Contrary to the general opinion fractures are by no means rare and usually result from trifling causes Spontaneous fracture not uncommonly first brings the patient to the attention of the physician Incomplete "fissure" fractures of the convex aspect of the bowed extremity are revealed often by the x ray Compression fracture of the spine may occur also The fractures in Paget's disease heal readily with abundant callus formation as in the normal

Difficulty in locomotion may occur particularly in cases where the changes in the bones result in pressure on the cerebellum, spinal cord or nerve roots Despite the marked changes in the skull psychiatric manifestations are not common Psychoses[9, 39], epilepsy and neurological symptoms due to compression of the spinal cord[17, 6] and of the brain[16, 18, 7] have been reported

Localized periostitis following trauma and nearly always of the tibia is present at some stage of the disease in a considerable percentage of cases A slight injury to the shin often results in an exquisitely tender and painful area which persists for months Spontaneous recovery takes place after a varying period

Joint complications of the type of true arthritis deformans or infectious arthritis have occurred so rarely with osteitis deformans that there seems no reason for accepting the view of some authors that the two conditions are related Almost constantly however the patient complains of stiffness and slight pain in the joints

Objective signs are excessively rare X rays commonly show a slight degree of osteoarthritis There is sufficient reason for regarding the subjective symptoms in the articulations as the result either of general senile changes or rarely of a true osteoarthritis

The occurrence of malignant disease especially of the bones with osteitis deformans has been emphasized repeatedly It is always a terminal complication occurring many years after the onset of osteitis Sarcoma is considerably more common than cancer and primary in the osseous system far more frequently than is metastasis from internal organs

In well marked cases of this disease lesions of the cardiovascular system are frequent[9] Most patients have arteriosclerosis and many have a very extraordinary degree of atheroma Mitral and aortic insufficiency and myocardial disease very often appear during the last years of life Apoplexy is one of the common causes of death

Bronchitis emphysema and pulmonary tuberculosis are the chief pulmonary

simulating the grotesque deformities of Paget's disease. The presence of the primary *disease in osteoarthropathy is also an important consideration.*

Cases of generalized osteitis fibrosa cystica (von Recklinghausen's disease) often bear a resemblance to Paget's disease inasmuch as the deformities may be somewhat similar. The disease begins much earlier in life in von Recklinghausen's disease and the skull is normal. The process in the bones in both diseases shows widespread absorption of lime and the formation of new fibro-osteoid bone but the pathological picture in the former is greatly modified by extensive *generalized decalcification as well as by cyst and tumor formation.* Spontaneous fractures are much more frequent. Instead of the regular bowing of the bones seen in osteitis deformans, *the deformities are characterized by angular curves* and multiple hyperostoses and the bones are greatly enlarged by tumors.

The elevated blood calcium and reduced inorganic phosphate content of the blood in osteitis fibrosa cystica as compared to the normal values observed in Paget's disease and the phosphatase values which rarely exceed 40 units in osteitis fibrosa cystica aid further in differentiating the two disorders. However rarely the two diseases may coexist in the same patient.[1] During a remission or *following parathyroidectomy the x ray appearance in the two disorders may* be very similar.

Localized syphilitic hyperostosis of the tibia may give a superficial resemblance to Paget's disease. The saber tibia of clinical monostotic Paget's disease resembles grossly diffuse non gummatous syphilitic involvement of the tibia. The x ray differentiates the two conditions, periosteal new bone of syphilis remaining distinct from the cortex which is not the case in Paget's disease. This difference may however disappear with time. In syphilis of the bone the marrow cavity tends to become more or less obliterated and filled by new bone, whereas in Paget's *disease it tends to become widened and uneven.*[1]

Melorheostosis results in expansion of the bones with an undulatory contour of the cortex but this disorder usually occurs in younger individuals than does Paget's disease, is unilateral and affects the long bones including the hands.[1] Osteopetrosis, hyperostotic meningiomas, neurofibromatosis and yaws when involving the bones also may simulate superficially the appearance of Paget's disease.

The alkaline serum phosphatase as first shown by Kay[1] is markedly increased in Paget's disease and serves as a useful laboratory aid in diagnosis. This *increased enzymic activity is not due to activation but to the actual presence of* large amounts of the enzyme in the blood.[7] In general the phosphatase activity *is proportional* to the progress of the disease, reaching values in advanced cases of 60 to 130 compared to 4 units in the normal. In early cases of the diseases values ranging from 4 5 to 8 5 are observed. The increase in enzyme activity also tends

From the true diffuse hyperostosis of the skull seen in leontiasis ossea Paget's disease is readily differentiated In the former the process consists in an enormous hypertrophy of the entire skull and especially of the bones of the face without involvement of other parts of the skeleton Leontiasis almost always begins in late childhood or in individuals under 30 years of age The phosphatase level in leontiasis is normal

Rickets bears no resemblance whatsoever to osteitis except in the bowing of the legs seen in adults as a result of the disease in childhood It is a disease of growing bones in early life and is concerned especially with the epiphyses and cartilages In general the changes in the bones in the two conditions bear no resemblance Likewise the x ray appearances of the bones in the two conditions could never be confused

Acromegaly often shows some changes in the long bones and these together with the enlargement of the skull and kyphosis may lead to confusion of the two diseases The process in the two conditions is entirely different in nature as well as in location In acromegaly the soft parts are chiefly involved and the enormous enlargement of the hands feet and face is never present in Paget's disease The calvarium remains unaltered and the long bones show none of the characteristics of the deformities common to osteitis The essential osseous changes are found in the small bones of the hands and feet Pain is absent

Osteoporosis senilis has been confused with Paget's disease but without reason as there is not even a superficial similarity in the two conditions The process in osteoporosis in the aged is general throughout the skeleton and is essentially an atrophy of the bone with absorption and resulting increase in its fragility No thickening or deformity of the long bones so characteristic of osteitis deformans occurs Pain is absent Osteoporosis may occur in Paget s disease as a secondary complication, particularly if the patient has been bedridden for some time

Osteomalacia may bear a superficial resemblance to Paget's disease The lesions in osteomalacia are most pronounced in the bones of the pelvis and are more strictly symmetrical When the long bones are involved, the regular curves of osteitis are absent and instead one finds angular curves resulting from fractures Atrophy of the bone is the predominating feature The x ray appearances are entirely distinct There are no cranial lesions The general posture is unlike that of Paget s disease

Secondary hypertrophic osteoarthropathy in its final stage has in a few recorded cases shown x ray appearances in the long bones somewhat suggestive of osteitis While the texture of the bone and general enlargement may be comparable there is no bowing The massive hands and feet with extreme clubbing of the fingers and toes invariably accompany such bone changes There is nothing

Osteotomy and corrective orthopedic procedures have not proved to be of value Where muscular atrophy due to disuse is present graduated exercises are of value The use of built up shoes is of help in overcoming difficulty in locomotion due to shortening of one leg Hearing devices are indicated for the deafness so commonly observed in the disease

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to remain constant over long periods in Paget's disease [9], which is not the case in most other disorders accompanied by an elevation in this function

High phosphatase values are encountered also in generalized osteitis fibrosa cystica and rickets but in these conditions the inorganic phosphate level of the serum is reduced and in the former the calcium is elevated, while in Paget's disease both calcium and phosphorus levels are normal (see Part I under Phosphatase Enzyme Activity) However these biochemical determinations although suggestive do not establish the diagnosis with certainty, since in early stages of the disease the values observed may not differ from those seen in generalized osteoporosis The serum phosphatase may be high also in osteoplastic metastatic carcinoma particularly when secondary to carcinoma of the prostate in which acid phosphatase in particular is increased The x ray findings are also very similar in these two conditions when the Paget's bone is of the sclerotic type[6] However the clinical findings and course of the process in the two diseases usually render their differentiation not difficult The serum calcium in Paget's disease is normal (9 to 11 5 mgm per 100 c c) as is also the inorganic phosphate (2 7 to 4 2 mgm per 100 c c) except in the presence of renal impairment [9]

TREATMENT

Numerous therapeutic measures have been advocated for the treatment of Paget's disease but none of these has proved to be of definite value The fact that the disease is subject to spontaneous remissions undoubtedly has been responsible for the apparent improvement noted by advocates of different forms of therapy Drugs such as arsenic potassium iodide and mercury are valueless Insulin and dietary control[41] and adrenal cortical extracts[68] have been advocated but there is no rationale for their use Lyon[33] recently has suggested the use of large doses of vitamin A In general the treatment is symptomatic

When the pain is severe sedatives and analgesics are required Salicylic acid derivatives bromides and other analgesics may be used As the pain usually is present for many years opiates should never be given lest the patient acquire the habit Local applications of heat often diminish the pain temporarily Irradiation of the affected bones with x ray has been advocated also [9] Headache and vertigo also may be treated by irradiation of the skull [9] In one case of intractable pain cobra venom gave relief [6]

Treatment directed to the improvement of the general nutrition are advisable The use of a diet high in calcium and phosphorus with the addition of vitamin D appears to be rational as an aid in preventing decalcification and softening of the bones However excessive doses of vitamin D should be avoided since these may give rise to metastatic calcification[41 6]

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Part III

CLUBBING AND HYPERTROPHIC OSTEOARTHROPATHY

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Introduction

Clubbing of the fingers and toes and secondary hypertrophic osteo-arthropathy are commonly occurring clinical phenomena which have long attracted interest but the pathogenesis of which remains obscure.

Synonyms. — Clubbed fingers, Hippocratic fingers, essential dactylomegaly, osteoarthropathie hypertrophiante pneumique, secundare hyperplastisches ostitis, osteoartropatia ipertrofica secondarie, toxigene osteoperiostitis ossificans, hypertrophic pulmonary osteoarthropathy, Marie's disease, Marie-Bamberger syndrome, Bamberger-Marie's disease, osteosis hyperplastica generalized, osteophytosis, hyperplastic or hypertrophic osteopathy or osteoarthropathy, peripheral hyperostosis, pachyperiostosis, ensheathing o teitis, acropachy, acro-elephentiasis ossea sive molle, osteitis hyperplastica. The clubbed fingers have been described also as drumstick, serpent's head or clock pendulum fingers. The nails of such fingers have been referred to as watch glass or parrot beak nails.

Definition. — A condition characterized by a usually painless general and symmetrical clubbing of the fingers and toes, often associated with hypertrophy of the long bones of the feet and hands and less frequently with painful enlargement of the long bones of the forearms and legs. The condition usually is secondary to some chronic, rarely acute, disease, most commonly of the lungs. Hereditary and idiopathic as well as unilateral and unidigital forms also occur.

Historical. — Simple clubbing of the fingers is mentioned in some of the earliest of medical writings. Hippocrates[4] particularly described the condition as occurring with advanced phthisis and empyema and emphasized the importance of these changes as diagnostic of purulent pleural effusion. Many of the authors following Hippocrates recognized the condition as found with many chronic diseases of the heart and lungs but always emphasized its importance as most frequently occurring with phthisis. In the nineteenth century the subject received

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of wild and domestic animals rat dog horse lion usually associated with some chronic pulmonary infection[3, 8]

Classification and Etiology

The varieties of clubbing have been classified into three main groups 1) symmetrical, 2) unilateral and 3) unidigital The first mentioned in turn may be subdivided further into hereditary idiopathic and acquired types Hypertrophic osteoarthropathy may occur with any of these varieties of clubbing

Hereditary Form

The great majority of cases of clubbing and hypertrophic osteoarthropathy are clearly secondary but a few cases occur without relation to any antecedent disease although without a postmortem examination it is impossible to exclude the existence of a primary disease Since in the overwhelming majority of cases Marie s disease is characteristically a secondary condition we are justified in demanding complete proof that any given example is primary

Clubbed fingers occurring in otherwise healthy people have been designated as familial or congenital clubbing[5] Neither of these terms is satisfactory for the former would apply to clubbing occurring in families several members of which were afflicted with tuberculosis or other diseases which predispose to clubbing[3] Congenital clubbing is a misnomer since the condition is inherited as a Mendelian dominant trait[3, 58] Hereditary clubbing is thus the proper designation for the condition occurring under these circumstances[38]

Idiopathic Symmetrical Form

Cases of clubbing with or without hypertrophic osteoarthropathy in which there is neither evidence of a primary disease nor of an inherited predisposition to the condition are designated as idiopathic[7] As already indicated the existence of such cases can be established only with difficulty Occurring as it does with such a variety of diseases it is to be expected that in some instances the evidence of the primary condition should be difficult to find or wanting Some obscure cardiac or pulmonary condition some focus of infection syphilis or liver cirrhosis might conceivably exist without being manifest

Acquired Symmetrical Forms

Acquired symmetrical clubbing associated in some cases with hypertrophic osteoarthropathy is in most cases observed as secondary to some chronic disease

much attention in medical literature and gradually an accurate knowledge developed as to the exact nature of the changes in the fingers and their significance[1] No alterations other than those in the fingers were ever mentioned by these writers until 1889 when von Bamberger[4] first described general thickening and sclerosis of the long bones associated with clubbing of the fingers, occurring late in the course of two severe cases of bronchiectasis In a second paper published in 1891 the same author discussed at length the nature and extent of these bony changes and their relation to various diseases He found an "ossifying periostitis" in the bones of the arms and legs in bronchiectasis, empyema, phthisis and cardiac diseases

Almost coincidently Marie (1891) published a very full and accurate description of the process in the long bones and fingers based on eight cases He considered the condition always secondary to some primary disease chiefly of the lungs and suggested the term "osteoarthropathie hypertrophiante pneumique" Because of this careful description the name "Marie s disease" has been applied frequently to this condition

In more recent years the subject has been widely studied, and a voluminous literature has accumulated Alexander[1] in 1906 collected 77 cases of unquestioned secondary hypertrophic osteoarthropathy and in 1915 Locke[13] assembled 144 typical cases Mendlowitz recently has reviewed the subject and presented the accumulated data with 337 references to the literature

Relation of Clubbed Fingers to Secondary Osteoarthropathy

In his second paper von Bamberger discussed the possible relationship of these two conditions and suggested that the former may be simply an early stage of the latter He based his conclusions on the fact that three of his cases which ante mortem gave no evidence of changes other than the clubbed fingers at autopsy showed periostitis of many of the long bones This view was opposed by many subsequent authors who held that there was a distinct difference between the two and that they should be regarded as independent conditions The evidence is preponderatingly in favor of Bamberger s view and may be summarized as follows[1] (1) both conditions are found associated with the same group of primary diseases (2) the type of clubbing is the same the differences described being merely the result of difference in the stage of the process (3) clubbing of the fingers invariably occurs in secondary hypertrophic osteoarthropathy (4) many cases which appear to be simple clubbing are shown by x ray examination to possess alteration in the long bones precisely the same as those seen in secondary hypertrophic osteoarthropathy

Hypertrophic osteoarthropathy has been observed also to occur in a number

Unilateral Clubbing

Clubbing limited to one extremity is encountered most commonly in aneurysm of the arch of the aorta the innominate or the subclavian artery Unilateral clubbing has been observed also in phlebectasia involving one extremity in recurrent subluxation of the shoulder in Pancoast tumors of the lung and in lymphangitis[34]

Unidigital Clubbing

Clubbing limited to a single digit has been described after local trauma to the finger, injury of the median nerve in Boeck s sarcoid in felons and in tophaceous gout It is necessary to distinguish trophic changes and bony deformities which may involve the fingers and simulate clubbing Bilateral unidigital clubbing especially of the thumbs is hereditary [8]

Pathogenesis

The actual cause of clubbing and secondary osteoarthropathy occurring as they do with such a wide variety of diseases has not been positively determined The multiplicity of antecedent diseases makes it difficult to assume any single factor present in all which can lead to the characteristic secondary alterations in the skeleton Several theories have been advanced to explain the changes found in the osseous system

The earliest view as to the origin of clubbing was that it was due to emaciation This view was discarded when it became evident that many patients manifesting the disorder were well nourished Pigeaux[44] in 1832 suggested that clubbing was a result of edema and increase of the connective tissue of the finger tips due to a deficient blood supply

Von Bamberger suggested the theory that the drumstick fingers and proliferative periostitis were the result of toxic absorption that were due to some chemical action In support of the theory of toxic origin he argued that clubbing of the fingers is never seen with simple catarrhal processes in the lungs and in phthisis only in the advanced stages when purulent expectoration is present Von Bamberger attempted to produce the lesions of osteoarthropathy in rabbits by injecting into the rectum sputum from a case of bronchiectasis but his results were negative More recent attempts to produce the condition in animals by the intravenous injection of pathogenic organisms were unsuccessful also Marie also advocated the toxic theory He believed that the lesions are the result of the production of putrid or fermented substances due to micro organisms which are absorbed into the circulation and through selective action exert an influence on

particularly of the lungs circulatory system, liver or gastrointestinal tract In 144 cases collected by Locke the primary disease involved the respiratory tract in 112, the gastrointestinal canal in 13 and the circulatory system in 6 Miscellaneous or unknown diseases were present in the remaining 13

Pulmonary — The condition may occur in any variety of pulmonary, pleural or mediastinal disease most commonly in chronic suppurative conditions such as bronchiectasis pulmonary abscess and empyema [14] It is found in protracted cases of pulmonary tuberculosis and in conditions producing a chronic pneumonitis It is seen in association with pneumonoconiosis atelectasis due to intrabronchial obstruction chest deformities due to rickets or Pott's disease, poliomyelitis paralysis of the diaphragm or diaphragmatic pleurisy It is rare in cases of pulmonary endarteritis but occurs in Ayerza s syndrome secondary to chronic pneumonitis Clubbing is seen only rarely in emphysema, in congenital cystic disease[4] chronic passive congestion of the lung or in acute pulmonary infections such as pneumonia Clubbing may occur in persons living at high altitudes but subsides on their return to sea level[41]

Clubbing occurs frequently in all varieties of primary and secondary neoplasms affecting the chest or its contents[1 10] It occurs also in aortic aneurysm[17]

Cardiac — Congenital disease of the heart with cyanosis is commonly associated with pronounced clubbing[1] When there is no cyanosis clubbing is not seen unless the condition is complicated by the presence of other diseases such as subacute bacterial endocarditis or bronchiectasis [3 5] Clubbing may be the first sign of subacute bacterial endocarditis[11] It is stated to be seen occasionally in mitral stenosis with chronic congestive heart failure but apparently is extremely rare in this condition

Hepatic — Clubbing frequently is found in association with diseases of the liver particularly with hypertrophic cirrhosis It is rare in other forms of hepatic cirrhosis

Gastrointestinal — Chronic disorders of the gastrointestinal tract, particularly those accompanied by diarrhea such as ulcerative colitis[40], dysentery[9], intestinal tuberculosis sprue or steatorrhea often are associated with clubbing When this occurs secondary to pyloric obstruction gastrectasia or infestation with worms, the clubbing may recede following cure of the primary disorder

Miscellaneous — In addition to the causes already cited clubbing and secondary osteoarthropathy have been described in association with a variety of other disorders e g following thyroidectomy in chronic cystopyelitis Raynaud s disease purpura and polycythemia vera Clubbing is rare in the last named condition The causal relationship between the clubbing and the primary disease manifested by the patient always is open to question since the possibility of an unrecognized area of bronchiectasis or other pulmonary lesion cannot be excluded

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certain parts of the bones and joints' It is evident from the fact that this disease occurs with certain heart lesions and other conditions, where no form of suppuration exists that the toxic theory alone will not fit all cases Von Bamberger argued that the majority of the heart cases recorded with clubbing of the fingers and periosteal changes also have lung complications, but admitted that local stasis may stimulate proliferation of bone and that in some of the cardiac cases, such as those of the congenital type the stasis alone may lead to the alterations in the end phalanges and long bones

Subsequent workers confusing hypertrophic osteoarthropathy with syphilitic periostitis suggested syphilis as the cause of the disorder Because of the analogy between the bone and joint changes in chronic tuberculosis and osteoarthropathy and the frequency with which the latter is secondary to tuberculous infection, many believed tuberculosis to be the etiological agent

Other theories in vogue at various times were the mechanical theory, according to which clubbing was due to capillary stasis for which, however, there is no valid evidence, and the anoxic theory according to which arterial or local anoxemia were the causative agents Various endocrine organs the thyroid, pituitary and gonads were incriminated among a welter of fantastic theories

The pathogenesis of clubbing has been elucidated to some extent by the recent experimental studies on animals and by physiological studies on the condition in the human Earlier attempts to induce the disorder in animals by injection of bacteria or toxins, by producing pulmonary abscesses by tying off bronchi or by causing chronic congestion failed Mendlowitz and Leslie[19] succeeded in producing hypertrophic osteoarthropathy in dogs by anastomosis of the left pulmonary artery to the adjacent left auricle This induced a shunt of 13 to 46 per cent of the ventricular output and simulated the circulatory status observed in congenital heart disease This was accompanied by an increase in systemic cardiac output with a relatively normal blood flow through the lungs

Studies of the blood flow through clubbed fingers shows this to be increased , the digital arterial blood pressure as well as the blood flow per square centimeter of finger tip surface remaining, however normal[37] Studies of the arterial venous and capillary blood pressures as well as direct observation of the capillaries have led to divergent results [9]

It would appear from the available data that active hyperemia with an increased blood flow through the extremities is necessary for the development of secondary osteoarthropathy Hyperemia alone will however not induce the condition for it is not seen in hyperthyroidism or other conditions in which the blood flow through the extremities is altered Another factor, possibly a decreased oxygen content of the arterial blood or the presence of toxic products which inhibit metabolic functions apparently must be present also to result in the disease



Fig 5 —Secondary hypertrophic osteoarthropathy male age 3 X ray of forearm showing characteristic irregular subperiosteal layer of new bone and especially the irregular and abundant proliferation of new bone about the epiphyses Original shaft unchanged

Pathology

The pathological picture in hypertrophic osteoarthropathy varies depending upon the nature of the primary disease and especially upon the degree to which the bones and joints are affected The difficulty of obtaining specimens uncom plicated by the associated primary disease has militated against exact studies of the process

End Phalanges —The typical bulbous enlargement of the terminal phalanges of the fingers and toes as seen in clubbing is due in part to an increased prolifera tion of all the soft tissues as well as an increased thickness of the periosteum and of the ungual process of the bone[1] In advanced cases however, atrophy and re sorption of the bone may occur [1, 9, 30] It must be borne in mind always that the ungual phalanges in healthy individuals present marked variations in size and shape Among 39 cases of apparently simple clubbing of the fingers studied by the x ray, Locke[15] found a definite proliferation of the distal phalanges in 5 Three occurred with chronic pulmonary tuberculosis one with cardiac disease and one with cardiac disease and pulmonary tuberculosis In the more advanced cases with changes in the long bones this hypertrophy in the terminal bones of the fingers is much more common and marked

The alterations in the end phalanges are in the nature of an irregular mossy proliferation confined chiefly to the distal half giving to the bone a ' burr like appearance Rarely very long spur like projections are observed

The changes in the soft parts are much more striking The nails are greatly thickened ridged longitudinally and curved in both directions sometimes to such a degree as to offer a very close resemblance to a parrot s beak The nail bed is full rounded smooth and injected A uniform thickening of the soft tissues gives to the part a bulbous appearance like the end of a drum stick hence the name so commonly applied of drum stick fingers Actual edema probably does not occur the enlargement being due to various factors including prolifera tion of connective and fatty tissue and an injection of the capillaries about the nail bed A slight amount of cellular infiltration has been described al o The finger ends usually are deeply cyanosed

In some of the cases of advanced hypertrophic osteoarthropathy the whole hand is enlarged in addition to the clubbing the fingers throughout their length being increased in size thus giving the same appearance as in gigantism

Changes in the Long Bones — It has been stated frequently that the process in the long bones does not begin for several years after the onset of the primary disease This observation is doubtless correct so far as the advanced stage of the disease is concerned but systematic x ray examinations of the bones of the forearms and lower legs in cases of clubbed fingers has revealed early changes

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in these parts as well as in the phalanges Of 39 cases of clubbed fingers studied by Locke[1] 12 showed characteristic subperiosteal bony proliferation of the same type and distribution as described in osteoarthropathy These changes in the long bones undoubtedly represent the early stage of that seen in the well developed cases of Marie s disease They may become evident clinically or demonstrable in the x ray within several months of the onset of the primary disease

The skeletal changes begin in the distal third of the diaphysis of the ulna and tibia but with the advance of the process other bones may become involved Those affected earliest and most frequently are the fibula, radius femur, humerus metacarpals and metatarsals Later the phalanges, clavicles and pelvis may be involved and the tarsals carpals, vertebrae, ribs and scapulae The mandible and skull are rarely affected[18]

The typical process in the bones (Figs 5 and 6) consists primarily in a slowly progressive ossifying periostitis beginning in the distal end of the diaphysis and later involving the entire shaft There is constantly a thickening of the periosteum which is deeply injected The layer of new bone is irregular in outline and appears as a distinct sheath enveloping the original shaft At first thin and poor in lime salts at a later stage of the disease it becomes dense and closely united with the cortical layer of the old bone As a result of this proliferation the bone is increased in size in rare instances to double its normal diameter As the disease progresses there develops hand in hand with the ossifying periostitis a rarefying osteitis of the old shaft which has been observed to proceed to such an extent as to destroy the normal structure and appearance This is the condition shown in the x ray reproduced in Fig 6 which except for the absence of bowing is quite similar to that seen in osteitis deformans At this stage the marrow space often is obliterated Suppuration never occurs Cysts are seen rarely Osteophytes near the costal cartilages are not uncommon

Beyond the early stages the epiphyses are involved along with the diaphyses, but the newly formed bone is of more irregular type and less dense than the old bone Its appearance is that of a thick uneven moss like, exuberant, new growth which stops sharply at the cartilage edge

Microscopically the periosteum is thickened and shows an increased proliferation of the cambium layer[18] It may show areas of hemorrhage and increased vascularity At a later stage when osteoporosis occurs increased osteoclastic activity is evident lacunae appear in the newly formed bone and the Haversian system becomes disrupted

Alterations in the soft tissues about the diseased bone are marked and quite unique The swelling is of such a high grade as to give to the forearms and legs



Fig 6—Secondary hypertrophic osteoarthropathy male age 32 X ray of leg Everywhere evidence of subperiosteal new bone formation which in the femur is sharply marked off from the old bone but in the fibula and tibia the original shaft is altered throughout and there is no demarcation between old and new bone

a clumsy cylindrical appearance This results largely from hyperplasia of the connective tissue but edema is also a factor Muscular atrophy of a high grade may be present especially in the hands

Joints —The involvement of the joints in osteoarthropathy is more constant than usually recognized perhaps due to the fact that it is a relatively late development In some instances the symptoms in the articulations are more prominent than those referable to the long bones In well developed cases the joints themselves participate to a considerable extent in the morbid process The joints most often involved are those adjacent to the affected bones i e the wrists knees ankles elbows and small joints of the hands and feet The articulations are enlarged to a varying degree principally as a result of the swelling of the periarticular tissues and the presence of fluid in the capsule The effusion is characteristically intermittent and often considerable in amount There is as a rule no local redness heat or acute tenderness The process is in the nature of a low grade synovitis with thickening of the capsules and a varying degree of erosion of the cartilage In a few cases the articular ends of the bones have been found completely denuded of cartilage though as a rule the cartilage is but little changed Ankylosis may occur rarely as a result of the bone proliferation in the neighborhood of the articulation[5, 3, 6]

Chemical Pathology —The earlier claims of abnormality in the chemical composition of the new bone formed in hypertrophic osteoarthropathy has not been confirmed by more recent studies[7]

Symptoms

Three clinical types of secondary hypertrophic osteoarthropathy usually are described following Sternberg s classification (1) clubbing of the fingers and toes without changes in the long bones Subjective signs and symptoms usually are wanting The condition may be secondary to any of the diseases discussed under etiology (2) von Bamberger s type of a higher grade namely a combination of clubbing with painful thickening of the long bones especially of the forearms and lower legs This type is secondary to the same diseases as is type 1 (3) Marie s type osteoarthropathie hypertrophiante or a stage of the disease where the condition is no longer a mere incident in the course of the primary disease but by reason of the conspicuous general deformities and severe symptoms itself comes to the foreground In this group according to Sternberg the primary disease often is not prominent and may even be undetermined

In the light of our present knowledge these groups are clearly but different stages in the development of the disease, which advances from one to another

to detect in their early stages The great toe appears to be disproportionately involved The enlargement affects both diameters of the finger tip giving it a globular or bulbous appearance Occasionally the increase in size is enormous Marie recording one case which measured 10 cm in circumference The skin may be more or less thickened appears shiny and may be pigmented More striking are the alterations in the nail It is curved both transversely and longitudinally thickened and frequently shows rather marked irregularities and prominent grooves running lengthwise of the nail Not infrequently the free end of the nail is sharply hooked over the finger end in form resembling a parrot s beak Other nutritional disturbances as indicated by increased brittleness are met with also In well developed cases the greatest prominence of the nail is at about its central portion Varying degrees of cyanosis of the nail are the rule The affected nails are said to grow more rapidly than normal The nail bed is raised abnormally smooth and deeply injected Pressure over the root of the nail gives a sensation of fluctuation as though the root were resting on a fluid cushion At this stage muscular atrophy in the fingers often accentuates the clubbing

With the approach of a later stage of the disease and accompanying the process in the long bones the whole hand becomes altered It appears gigantic crude and ' paw like The fingers look puffy and sometimes are moderately spindle shaped They seem stiff are handled clumsily muscular power is greatly diminished and the hand cannot be closed completely The general appearances in the hands suggest the presence of arthritis in the joints of the fingers and metacarpo phalangeal joints but aside from a moderate thickening of the periarticular tissues and slight stiffness or very moderate dull pain there is no real evidence of an actual arthritis Quite analogous changes occur in the feet but are less evident in the toes than in the tarsus and ankle Von Bamberger aptly has suggested the term ' elephant foot ' for the most extreme type of deformity in the foot The hands and feet are moist from excessive sweating

When the long bones are involved the clinical picture becomes a more complicated one and the symptoms are no longer solely objective Pain is the most prominent and constant symptom and generally develops with the appearance of swelling in the legs and forearms to which region it is almost invariably confined It is variously described by the sufferers as a mere discomfort a burning or prickly sensation or more commonly as a deep dull ache in the bones which for a considerable time at least increases in severity as the di ease advances In some of the cases of long standing the pain may disappear entirely It is apt to be intermittent occurring for short intervals or only at night or in the legs after long standing More rarely the pain is constant and agonizing and may resemble the exquisite pain and tenderness so commonly observed in rheumatic fever Cold

grade Any attempt at definite grouping of cases, as suggested by Sternberg, except for purposes of description is both unnecessary and confusing

The changes in the ungual phalanges vary from the beginning thickening in the soft parts occurring without involvement of the long bones, to the most extreme type of clubbing accompanying advanced stages of the disease When the disease is well established the alterations in the finger ends are very striking though by reason of the absence of any subjective symptoms the patient

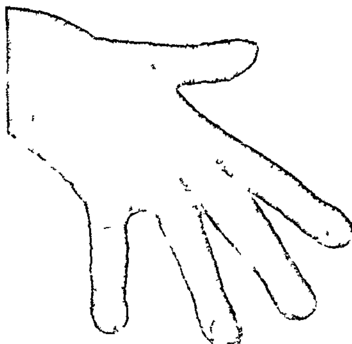


FIG , —Clubbed fingers The fingers in a 35 year old patient suffering from chronic bronchiectasis Note the parrot beaked nails of the clubbed fingers

usually is entirely unconscious of their presence The onset of these changes is insidious As a rule slowly progressive they may in rare instances as with a closed empyema develop with extraordinary rapidity and well marked clubbing be present in the course of a few weeks A case in an infant has been described [8]

In the average case of simple clubbed fingers the deformity is sharply confined to the distal phalanx (Fig 7) and is almost strictly symmetrical the two hands showing equal involvement Changes in the toes accompany those in the fingers but, due to the frequent misshapen form of the toes are more difficult

may be of pain and stiffness in the articulations usually the wrists and ankles Actual inflammation of the joints is seen in exceptional cases The acute symptoms in the joints usually are associated with an elevation of temperature which subsides coincidently with the disappearance of the symptoms Thompson observed enlargement of the lymph nodes in the axilla and groin associated with the acute stage of the process in the wrists and joints of the lower extremity He regards the process in the joints in all cases as unquestionably inflammatory in type Subluxation or other forms of dislocation are unknown although a slight degree of hyperextension may occur There is no grating in the affected joint

Painful swelling of the breast similar to that seen in males at the time of puberty was noted in one case by von Bamberger Others have described bulbous enlargement of the nose ears eyelids and thickening of the malar region Skin lesions are rare, but ichthyosis eczema erythema pigmentation and rapid growth of hair may occur occasionally Visceral disturbances except as associated with the primary disease are unknown There is no reaction of degeneration in the muscles no change in the reflexes and no sensory disturbance

The course of the disease is like its clinical types extremely varied and probably depends entirely on the course of the primary disease All symptoms and signs may disappear if the lesions in the lungs or elsewhere producing them are cured Rarely the disease follows a chronic progressive course without discoverable activity in the antecedent disease At times after a period of activity of many months or a few years it subsides into a quiescent state Ordinarily the course throughout is with periods of alternating activity and inactivity The duration often is many years since the disease being a secondary condition has no direct influence on the general health

Diagnosis

Diagnosis presents no difficulties since the well marked lesions of osteoarthropathy can hardly be confused with any other disease Clubbing of the fingers should lead always to an examination of the bones of the hands and feet as well as those of the forearms and legs It is only by this means that it is possible to detect the early stages of the periosteal proliferation so characteristic of the disease The fairly regular sheath of new bone is met with in no other condition The combination of the clubbed fingers and painful thickening of the long bones showing the peculiar subperiosteal layer of bone by x ray and their occurrence with some diseases of the lungs and rarely with other conditions are pathognomonic of the disease[3]

The resemblance of this condition to acromegaly is only a superficial one Acromegaly is a primary disease The peculiar changes in the face are wanting

accentuates and warmth relieves the pain The patient usually finds that the pain in the arms and legs, as well as the swelling, is worse during the periods when the primary disease is most active, as in the case of bronchiectasis or lung abscess when the sputum is most abundant and purulent The symptoms of the secondary disease thus run a course parallel to that of the underlying disease Occasionally however an exacerbation of the secondary hypertrophic osteoarthropathy may occur in the absence of any evidence of a change in the primary condition Sensitiveness over the enlarged bones always accompanies the pain[51]



Fig 8—Secondary hypertrophic osteoarthropathy Male age 30 Observe the clubbing of the fingers and toes and the marked cylindrical enlargement of the lower legs and forearms

The evidence of bone involvement begins in the distal third of the forearm and lower legs, and it is in these regions that the process reaches the most extreme degree When fully established the whole forearm and lower leg are cylindrically enlarged and of about the same diameter throughout (Fig 8) A moderate degree of edema may be present, and in the most acute cases some local increase in temperature is associated with the pain and tenderness In its extreme development that is, when the osseous system is generally affected the disease presents a very unusual picture General and extreme emaciation is present likewise a considerable degree of anemia The patient is weak, holds himself stiffly and moves about clumsily as a result of stiffness in the spine and joints Kyphosis of varying degrees may exist

A more or less general involvement of the joints similar to arthritis in the hands accompanies the late stages of the disease[8] Those joints adjacent to the most marked osseous changes are the ones showing the most signs i e, the wrists and ankles The principal and the first complaint

may be of pain and stiffness in the articulations usually the wrists and ankles Actual inflammation of the joints is seen in exceptional cases The acute symptoms in the joints usually are associated with an elevation of temperature which subsides coincidently with the disappearance of the symptoms Thompson[34] observed enlargement of the lymph nodes in the axilla and groin associated with the acute stage of the process in the wrists and joints of the lower extremity He regards the process in the joints in all cases as unquestionably inflammatory in type Subluxation or other forms of dislocation are unknown although a slight degree of hyperextension may occur There is no grating in the affected joints

Painful swelling of the breast similar to that seen in males at the time of puberty was noted in one case by von Bamberger[3] Others have described bulbous enlargement of the nose ears eyelids and thickening of the malar region Skin lesions are rare but ichthyosis eczema erythema pigmentation and rapid growth of hair may occur occasionally Visceral disturbances except as associated with *the primary disease are unknown* *There is no reaction of degeneration in the* muscles no change in the reflexes and no sensory disturbance

The course of the disease is like its clinical types extremely varied and probably depends entirely on the course of the primary disease All symptoms and signs may disappear if the lesions in the lungs or elsewhere producing them are cured Rarely the disease follows a chronic progressive course without discoverable activity in the antecedent disease At times after a period of activity of many months or a few years it subsides into a quiescent state Ordinarily the course throughout is with periods of alternating activity and inactivity The duration often is many years since the disease being a secondary condition has no direct influence on the general health

Diagnosis

Diagnosis presents no difficulties since the well marked lesions of osteoarthropathy can hardly be confused with any other disease Clubbing of the fingers should lead always to an examination of the bones of the hands and feet as well as those of the forearms and legs It is only by this means that it is possible to detect the early stages of the periosteal proliferation so characteristic of the disease The fairly regular sheath of new bone is met with in no other condition The *combination of the clubbed fingers and painful thickening of the long bones show*ing the peculiar subperiosteal layer of bone by x ray and their occurrence with some diseases of the lungs and rarely with other conditions are pathognomonic of the disease[35]

The resemblance of this condition to acromegaly is only a superficial one Acromegaly is a primary disease The peculiar changes in the face are wanting

in osteoarthropathy The hands may be enlarged and clumsy in osteoarthropathy but do not stimulate the appearances seen in acromegaly Symptoms referable to the central nervous system eyes and metabolic functions are never present in osteoarthropathy Clubbing is rare in acromegaly, and the nails are small The alterations in the long bones as seen in x rays are seldom pronounced and consist merely in an irregularity of outline especially in the epiphysis and an accentua tion of the prominences marking the muscle and tendon attachments

In occasional cases where the joint symptoms are most pronounced, the osteo arthropathy may be mistaken for chronic arthritis The joints however very seldom show any outspoken evidences of inflammation, and the deformities so common to chronic arthritis are lacking Clubbing of the fingers and thickening of the long bones are never seen in arthritis

Heberden s nodes likewise should never be confused with osteoarthropathy In this condition clubbing is wanting and the enlargement is not in the distal portion of the end phalanx but about the joint which is deformed These nodes are due to an osteoarthritis of the joint with hypertrophy of the bone which takes the form of osteophytic outgrowths on the dorsal surface at the edge of the joint cartilage The process is observed only in old or middle aged people and is a primary affection

Treatment

No form of therapy has any direct effect on the condition itself, though as mentioned above relief of the underlying disease often leads to prompt improve ment in the bones and finger ends For the pain treatment by the application of heat in some form or counter irritation is indicated Analgesics may be required in the rare cases with pain of an intense type The general treatment is the same as that for any chronic debilitating disease

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1900 The association of deafness with blue sclerae and brittle bones in the more complete form of the disease was pointed out by van der Hoeve and de Kleyn[2] in 1916

Incidence — The disease probably is not as rare as is usually assumed Gurlt s Handbuch published in 1862 contains an exhaustive discussion of the condition summarizing the cases recorded to that date and indicating the relation of the disease to other osseous affections of fetal and early life Griffith[9] in 1897 collected 67 and Ostheimer[4] in 1914 an additional 126 cases from the literature

Riesenmann and Yater[44] found 32 members of seven families with the disease residing in or near Washington D C The disease had occurred in 91 individuals among a total of 255 members of this group It is not unusual to discover a number of patients suffering from the disease in any large hospital devoted to chronic orthopedic disturbances in children[7,9,11,37]

Sex — Males are affected more frequently than females in the ratio of three to two[5]

ETIOLOGY

Fragilitas ossium is only one manifestation of a familial and hereditary disorder characterized by a congenital hypoplasia of the mesenchyme[8] The exact genetic relation between the fragility of the bones the blue sclerae and the defective hearing which constitute the most important pathological states in the complete syndrome still is a matter of controversy Some observers have assumed the existence of a genotypical relationship between the several pathological states due to linkage of several defective genes in the same chromosome[1] According to this view the occurrence of any combination of fragility of the bones blue sclerae and deafness would depend upon the particular defective genes which happen to be associated in a given case

Certain families manifest a predilection for deafness and for fragility of the bones which would favor the genotypical relationship outlined above However in most cases there is a considerable variation in the occurrence of the different components of the complete syndrome each of which may occur alone or in association with one or both of the others

Blue sclerae are present in 90 to 100 per cent of the individuals harboring the defective chromosome brittle bones are present in 50 to 65 per cent and deafness in only 25 to 43 per cent[1,4] The variation in the occurrence of the symptomatic triad in different generations of affected families suggests that a single gene only is defective This single gene is capable of variable expression and thus gives rise to the unpredictable association of the different symptomatic expressions of the disease[4]

Part IV

FRAGILITAS OSSIUM
(*Osteogenesis Imperfecta*)

Introduction

Definition — Fragilitas ossium is a rare congenital hereditary and familial disease of the skeleton characterized by an abnormal fragility of the bones which results in frequent fractures and deformities It is associated in some cases with blueness of the sclerae dislocation of the joints defective hearing and other evidences of hypoplasia of the mesenchyme

Synonyms — Osteopsathyrosis idiopathica osteogenesis imperfecta brittle bones and blue sclerae hereditary hypoplasia of the mesenchyme Eponyms applied to the condition are Lobstein s or Vrolik s disease, when fragility of the bones is present and van der Hoeve s syndrome when deafness is present also

Earlier workers confused the condition with rickets osteoporosis and osteomalacia using such terms as fetal rickets rachitis annularis osteoporosis fetalis, osteomalacia congenita and myeloplastic malacia to designate the condition Others indicated their assumed etiology of the disease by designating it as periosteal dystrophy or dysplasia pseudochondritis or chronic parenchymatous ostitis

The term fragilitas ossium is not entirely satisfactory since it denotes only one manifestation of the disorder *Hereditary hypoplasia of the mesenchyme* more accurately describes the syndrome in its entirety[3, 31 36]

Historical — Cases of fragilitas ossium were described first during the eighteenth century by Amand and by Ekman[14], but it was not until 1833 that von Lobstein[18] gave an accurate clinical description of the condition He noted the hereditary tendency of the disease and designated it as osteopsathyrosis idiopathica Vrolik[31] in 1849 published descriptions of the alterations occurring in the bones and suggested the term osteogenesis imperfecta

The occurrence of blue sclerae was noted first by Henzschel[4] in 1831 but their association in the same family and frequently in the same patient with fragility of the bones was reported first by Spurway in 1896 and Eddowes[13] in

PATHOLOGY

Fragilitas ossium is only one manifestation of a generalized defect in develop ment of the mesenchymal tissues[4,15] In addition to the bones abnormalities occur in the eyes ears muscles fasciae ligaments tendons blood vessels and con nective tissues generally

Bones — The bones show a characteristic thinning and atrophy which result in their abnormal fragility They are incompletely ossified with diaphyses soft and brittle Because of their extreme fragility numerous fractures occur spon taneously or as a result of the slightest trauma The e result in marked angular deformities Although the bones develop normally in length they tend to become shortened as a result of the bowing and deformities which follow fracture

The skull usually is normal in size and shape but there is often defective calci fication of the cranium which may in severe cases be a membranous sac calvaria membranacea consisting of a mosaic of tiny irregular islets of bone The b ne of the face and ba e of the skull usually are normal

The spine often is deformed The pelvis may become markedly distorted (Fig 9) as in osteomalacia The ribs are delicate and brittle undergoing re peated fractures

The long bones show the most marked deformities They are slender and thickened at the ends but approximately normal in contour if no fractures occur The cortex is thin and the trabeculae absent or present only as small irregular fragments The periosteum is thin and inactive The marrow spaces are en larged Fractures of the long bones or ribs are of the splintering type with com paratively *little displacement and without rupture of the periosteum There is* usually good callus formation with annular thickenings at the site of fracture which give the bones the appearance of a bamboo rod

On section the shafts of the bones are soft and porous the epiphyses and epiphyseal cartilages are relatively normal except late in the disease when degen erative changes may appear Microscopical examination reveals a loss of the normal architecture of the bone The Haversean canals appear as wide spaces interspersed between which are found embryonal osteoid tissue devoid of lamellae There is an absence of the normal osteoblasts which are replaced by fibroblasts chondroblasts and transitional cells In severe cases no osteoblasts may be pres ent at the zone of calcification Such osteoblasts as do occur are found towards the diaphysis and appear to be non functional[6]

Sections through an area of callus formation may reveal cartilaginous tissue with areas of necrosis There is puckering of the cartilage with widening of the zone of ossification Necrotic areas of calcified bone may be found in the di aphyseal portions of the bone Histologically the changes in the bone and carti

The inheritance factor in the disease follows the Mendelian law appearing as a dominant characteristic. The majority of the cases show a definite family history with many members affected during the course of successive generations[6, 8]. The disease sometimes may disappear for one, two or perhaps three successive generations to reappear again in the succeeding generation. Occasionally cases appear which seem to have arisen spontaneously with no evidence of inheritance[43]. Although such cases may conceivably have arisen spontaneously[44], it is more likely that they are due to the existence of a recessive characteristic in the hereditary pattern[4].

Both the male and female may transmit the disease. If only one parent is a carrier of the defective gene half of the children may be expected to have some manifestation of the disease.

Classification

Several classifications have been devised in an attempt to differentiate clinical varieties of the disease. Some designate as osteogenesis imperfecta those instances in which the disease occurs without evidence of its inheritance and reserve the term, fragilitas ossium to designate the obviously inherited form. Such a differentiation is unsound since both varieties are fundamentally the same insofar as their clinical manifestations are concerned[46].

The simplest classification is that originally suggested by Looser[39]. He differentiates three types of the disorder 1) osteogenesis imperfecta congenita in which the disease is evident at birth 2) osteogenesis imperfecta tarda in which it appears during infancy or early childhood and 3) idiopathic osteopsathyrosis in which blue sclerae are absent, and fragility of the bones first appears during childhood. This classification has value only for purposes of description and reflects no fundamental difference in the nature of the disorder except as to its severity.

Fragilitas ossium represents a disease entity which may occur in various forms depending upon the severity of the disease and the number of the mesenchymal defects associated with it. One may recognize a fetal or congenital form variously designated as osteogenesis imperfecta congenita or fetal osteopsathyrosis in which the fractures occur during intrauterine life. The child often is born prematurely or dead and survives at most a few years.

When the disease makes its appearance first during childhood or in adult life, it is designated as osteogenesis imperfecta tarda or idiopathic osteopsathyrosis. Unquestionably the varieties of the disease merely represent degrees of severity of the same disorder as there is no essential difference in the disease as seen at different ages.

lages in the severe congenital forms of the disease bear a superficial resemblance to that seen in infantile scurvy[5]

Eyes —The characteristically blue sclerae result from the thinness and translucency of this structure which permits the underlying choroid to be visible The cornea is also thin and may lack Bowman s membrane[11, 1]

Ears —The deafness is due to otosclerosis or atrophy of the labyrinth [8] The pinnae of the ear also may develop defectively and remain small and pointed

Other Tissues —The muscles show fatty infiltration and phanerosis The ligaments tendons and fasciae may be poorly developed and the joints lax and mobile[1, 48] as a result of hypoplasia of the connective tissue The walls of the blood vessels are weakened resulting in varicosities

There are no distinctive findings in the blood The calcium phosphorus and phosphatase levels are essentially normal Only occasionally is enlargement of the parathyroids encountered but in most cases no abnormalities are observed in any of the endocrine organs [5]



Fig 10 —The legs in fragilitas ossium To show the characteristic angulation of the deformed extremities in the patient shown in Figure 9

SYMPTOMATOLOGY

Fragilitas ossium is a developmental disorder which is marked usually by no constitutional symptoms except those induced secondarily by the osseous de



FIG 9—Patient with fragilitas ossium Note the marked crippling resulting from repeated fractures (Reproduced through courtesy of Dr W M Roberts and the North Carolina Orthopedic Hospital)

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formities and general hypoplasia of the tissues derived from the mesenchyme In the most severe form of the disease, in which it is present at birth there seems to be a general constitutional inferiority as a result of which the patient succumbs to the effects of malnutrition and infection

In the infantile form of the disorder the head usually appears large compared to the body The occipital frontal and temporal regions may protrude The ears may be small and pointed giving the patient an ' elf like ' appearance The extremities are small delicate and deformed (Fig 10) Due to the multiple deformities dwarfing results The abdomen may be protuberant The skin usually is pale and delicate Scoliosis and lordosis may result from the spinal curvature which is present

The eyes in cases showing blue sclerae are of an azure or deep blue tint which may vary from that of a robin s egg to a deep slaty color There is no correlation between the intensity of the discoloration of the eyes and the severity of the disease Corneal astigmatism is common The blue sclerae may be the only indication of the existence of the disease this defect being present in almost 100 per cent of the cases of whom only about one half will manifest characteristic fragility of the bones

The joints may be enlarged with hypermotility due to laxity of the ligaments and double jointedness Sprains and recurrent dislocations[1] are common Weakness of the transverse arch of the feet gives rise to pes planus

Deafness occurs in about one quarter of the patients This may be due to progressive otosclerosis or failure of development of the labyrinth Although otosclerosis usually is not fully developed before the age of thirty difficulty in hearing may appear first in late childhood and develop progressively thereafter *Tinnitus is a symptom* in about two thirds of those suffering from deafness, vertigo in about one tenth The deafness is of the conduction type

The muscles may be weak and hypotonic Atrophy both primary and secondary to disuse may occur As a result of atrophy of the middle coat of the blood vessels the superficial veins of the head may be prominent, and varicosities of the legs may result in swelling of the lower extremities[14]

Fractures

Multiple fractures are the constant and most characteristic symptom of brittle bones *The fractures* may be present at birth or develop in infancy or early childhood They result from slight violence and even with careful handling can not be averted in the severe congenital form of the disease The fractures lead to marked deformity and crippling (Figs 11 and 12) They are bilateral usually although in an occasional case only one side is affected In most instances

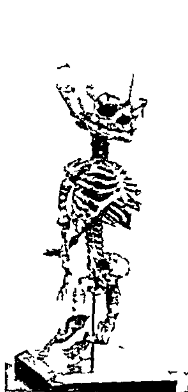


Fig 11

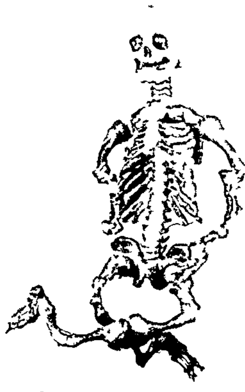


Fig 12

Fig 11 —Fragilitas ossium (osteopsathyrosis congenita) Skeleton of seven months fetus Note the innumerable fractures (Warren Museum Harvard Medical School)

Fig 12 —Fragilitas ossium Adult form Skeleton of woman of 1 Note multiple fractures and resulting deformities (Warren Museum Harvard Medical School)

many bones are fractured but at times only a single bone may undergo repeated fractures despite the x ray evidence of generalized osteoporosis throughout the skeleton[33] The local reactions of crepitus pain swelling tenderness and muscle spasm so characteristic of fractures in normal bones usually are ab ent or only very slight

There is a tendency for the fractures to recur at or near the same site This may be due in part to the deformity which results on healing[1] Callus usually is well formed but in many cases consists of fragile bone[31]

X Ray Findings

The x ray findings are distinctive and show a generalized osteoporosis uniformly affecting the entire skeleton The shafts of the long bones are thin in contrast to their expanded extremities which appear large because of the narrow diaphyses and normal epiphyses The cortex of the bones is reduced at times to a thin line The lamellae are sparse and thin The spongiosa of both epiphysis and diaphysis is faint with an absence of normal markings The medullary cavity may appear irregular and dilated A peculiar transverse cross striation of the long bones is seen often[44] Variations in the density of the bones often gives a mottled appearance[47]

Deformities usually of the angular type are evident where fractures have occurred Only rarely is bowing observed Excessive annular rings of callus may be present

Course and Prognosis

The course and prognosis varies with the type and severity of the disease In the congenital type the infant may be still born If alive it is a helpless cripple and usually succumbs within a few months[4,53] However, survival to the second or third year may occur occasionally as in the case described by Wilton[5]

In the infantile type of the disease the patient is normal at birth but develops fractures and deformities soon thereafter or when walking is attempted The later the symptoms appear the more hopeful the prognosis fractures becoming less frequent with increasing age Most of the fractures occur during the first seven years of life They are infrequent between the ages of 7 and 15 and only rarely occur in adulthood In Ostheimer's[40] series three quarters of the fractures occurred before the twenty second year There is an apparent remission in the disease insofar as fragility of the bones is concerned, at puberty In adults even x ray evidence of the disease may disappear due to the reversible nature of the process affecting the bones Those patients who pass through adolescence with relatively little deformity may lead a fairly active life and live to advanced age However fractures may occur as late as the fifth decade of life and very rarely thereafter[41]

The blue sclerae and other abnormalities of the eye are permanent but except for corneal astigmatism give rise to no disability Defective hearing may appear during childhood and progress to complete deafness[4]

Diagnosis

The disease rarely presents a problem in diagnosis The family history blue sclerae and evidence of multiple fractures following slight trauma or occurring

spontaneously leaves little question as to the diagnosis Where dwarfism ensues the condition may be confused with achondroplasia but the absence of the typical achondroplastic facies and the evidence of fractures which are absent in achondroplasia readily differentiate the two conditions The x ray examination also is entirely different showing the epiphyseal changes in achondroplasia in contrast to the abnormal diaphyses seen in fragilitas ossium

Severe rickets in an infant might be confusing but the history of dietary deficiency and if necessary the x ray differentiate the two diseases Fractures are rare in rickets and when they occur are the result of trauma are not intraperiosteal and are accompanied by slight callus formation Fractures in fragilitas ossium are intraperiosteal and callus formation is normal Congenital syphilis of the bone is primarily an osteochondritis while late syphilis results in thickening of the cortex[3]

An increased fragility of the bones with spontaneous fracture may occur in a variety of diseases malignancy of bone senile osteoporosis Paget s disease of bone osteomyelitis tuberculosis of the bone generalized osteitis fibrosa cystica and other cystic involvements of bone syringomyelia and other trophic neurological diseases but in these conditions the obvious alterations in the bone due to the primary disease usually is evident[17]

The blue sclerae are pathognomonic of the disease A similar discoloration may however be encountered in tuberculosis severe anemia metallic poisoning and sometimes in normal young infants and negro children[14]

TREATMENT

Prophylactic measures such as the application of braces to the lower extremities to prevent fractures are the most important part of therapy Fractures when they occur should be treated promptly and adequately to avoid deformities Osteotomy and osteoclasis with the use of homologous bone grafts[4] where necessary to affect good union are indicated in cases of deformity Successful results have been obtained by the use of these orthopedic measures in cases of ununited fractures and in otherwise hopeless cripples[9]

Earlier workers suggested the administration of elementary phosphorus (0 6 mgm) calcium phosphate (0 5 gm) and cod liver oil (4 c c) twice daily Since elementary pho phorus tends to sclerose the growing ends of the bone and does not affect the cortex its use would appear to be irrational More recently the use of thymus extracts and other endocrine products has been advocated However the assumption that the thymus is involved in osseous development is unsound[1] and hence there is no rational basis for the use of thymic extracts

The eyes in cases showing blue sclerotics require no treatment Corneal

astigmatism may require the use of spectacles The deafness, which is of the conduction type may be helped by hearing aids

Patients with the disease should be impressed with the hereditary tendency of the disease and the probability of half of their offspring being affected with the disorder

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Part V

OSTEOMALACIA

Introduction

Definition — An acquired disease of a chronic progressive type resulting from a deficiency of vitamin D and calcium and characterized by distinct metabolic and pathological changes in the bones Rheumatic pains in the back and legs are the first presenting symptoms Later as a result of marked softening and increased flexibility of the bones deformities occur

Synonyms — Adult rickets adult spasmophilia hunger osteopathy softening of the bones mollities ossium malacosteon The term is used frequently for softening of the bones generally but should be limited to the specific disease resulting from calcium and vitamin D deficiency

Incidence — Osteomalacia in its fully developed form has a definite geographic distribution It is observed only rarely in the Americas It is endemic in northern India[15] Algeria[1] North China[14] and Japan and occurs sporadically in parts of Europe During times of famine such as occurred in continental Europe after World War I it was prevalent and known as hunger osteopathy [4]

Repeated pregnancies and prolonged lactation predispose to the disease Hence it is more common in women in whom it occurs with greater severity with each succeeding pregnancy In the United States of America it is seen most often in association with chronic steatorrhea[3] The disease is rare in tropical countries where the inhabitants are exposed to sunshine However among the Mohammedans where the women observe strict purdah and in metropolitan areas where access to the sun is limited the disease tends to occur among those on a poor diet[3] The disease is apt to occur in individuals on a vegetarian diet without milk or eggs particularly if they live under poor hygienic conditions without access to sunshine[9, 5]

Pathogenesis

Older theories assumed that the disease was the result of hyperactivity of the ovaries hyperemia of the bones a deficiency of epinephrine infection due to un

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lactation will deplete rapidly the maternal skeleton unless supplied by an adequate intake of calcium phosphorus and vitamin D Where the diet is poor in calcium and vitamin D and the period of lactation is prolonged as in Oriental countries osteomalacia develops

A common cause of sporadic osteomalacia as observed in this country is chronic steatorrhea In this condition there is a failure of absorption of vitamin D and an increased fecal excretion of calcium due to the formation of insoluble calcium soaps A similar condition occurs in chronic obstruction of the bile duct which may result al o in the development of osteomalacia[30] An increased acidity of the contents of the gastrointestinal tract hypermotility of the bowel or an abnormal calcium phosphorus ratio in the diet all of which interfere with the absorption of calcium will predispo e also to the development of osteomalacia Where the disease is present in latent form even a slight renal failure may suffice to disturb the calcium phosphorus metabolism sufficiently to induce manifest osteomalacia[31]

Only rarely is osteomalacia attributable to a single factor although vitamin D deficiency is operative in all cases In most cases in addition to the avitaminosis one or more of the factors which have been discussed initiates the appearance of the disease

PATHOLOGY

The first recorded necropsy for scientific purposes in the New World was performed by Cadwalader in 1742 on a patient suffering from osteomalacia [8] The extremities of this patient as described by Cadwalader were for several months before her death as limber as a rag and would bend any way with less difficulty than the muscular parts of a healthy person s leg without the interposition of the bones This is an apt description of the marked softening of the bones occurring in advanced cases of the disease

The primary disorder in osteomalacia is a loss of the mineral elements from the skeleton as a result of which the bones become soft and flexible They are not fragile and hence fractures are infrequent but bending and deformity occur In milder cases no gross skeletal changes may be evident although examination by x ray reveals marked osteoporosis The loss in mineral content in osteomalacia is accompanied by an actual increase in the amount of organic matter present in the bones The formation of osteoid tissue proceeds normally failure of mineralization of this matrix being the primary disorder in the disease This results in the observed softening of the bones which may be cut easily with a knife Due to their flexibility the bones become bowed irregularly with angulation in contrast to the even bowing observed in Paget s disease

hygienic living conditions the presence in the blood of abnormal amounts of organic acids which dissolved the bones disease of the thyroids, parathyroids or pituitary or an hereditary congenital disorder It is only during the last two decades with the advance in our understanding of the function of vitamin D in relation to calcium metabolism that the pathogenesis of the disorder has been clarified It is now clear that osteomalacia is the adult counterpart of rickets and that it is due to the same cause as the latter, namely, a deficiency of vitamin D and calcium

The apparent difference in the clinical and pathological manifestations of rickets and osteomalacia is accounted for by the fact that the former occurs at an age when growth processes in the bones are active The proliferative change in the epiphyseal junction characteristic of rickets is not possible in osteomalacia which occurs after closure of the epiphyses has taken place It is only at the costochondral junctions where cartilage remains in intimate connection with bone even in adulthood that the same changes are found in osteomalacia as occur in the epiphyseal discs of children suffering from rickets[a]

Vitamin D is essential for the proper absorption and utilization of calcium and for its deposition in the bones (see Part I of this Chapter) Hence the availability and requirements of the organism for calcium will play an intimate role in any disorder resulting from vitamin D deficiency The two factors vitamin D and calcium must be considered together in explaining the pathogenesis of osteomalacia[3] A deficiency of vitamin D, even when the calcium and phosphorus intake is relatively normal will result in osteomalacia as in the patient reported by Schultzer [3] In most instances however a diet deficient in calcium or other factors causing a deficiency of this element superimposed upon a deficiency of the vitamin, is responsible for the development of the disease

Normally exposure to the sunlight suffices to protect the adult from a deficiency of vitamin D even where foodstuffs rich in this vitamin are not ingested Among sects in which the women may not appear in the outdoors exposed, purdah, and in northern climates where access to the sun is brief during the winter months a deficiency of the vitamin may be incurred easily unless the diet is rich in this essential When, in addition, the dietary intake of calcium is low or there is an exorbitant demand for this element osteomalacia is apt to develop

It has long been recognized that repeated pregnancies and prolonged lactation predispose to the development of osteomalacia which tends to become progressively worse with each gestation This is the so called puerperal form in which osteomalacia is encountered most commonly[4] During pregnancy approximately 20 to 30 gm of calcium are drained from the maternal organism for the fetus During the early months of lactation 250 to 350 mgm of calcium are excreted into the milk daily This large demand for calcium during gestation and



FIG 13 —Osteomalacia skeleton of adult (Warren Museum Harvard Medical School)

In the more severe cases of osteomalacia marked deformities of the entire skeleton occur The spine becomes deformed with expansion of the intervertebral discs into the body of the vertebrae This converts the latter into biconcave discs the so called fish vertebrae Kyphoscoliosis and lordosis are common which together with the compression of the vertebrae result in a loss of height of the patient and sinking of the head upon the chest (Fig 13)

The pelvis is markedly deformed with protrusion of the symphysis anteriorly, giving rise to its duck billed form The sacrum is forced down by the weight of the body while the pelvis is compressed laterally forcing the ischial tuberosities together The outlet of the pelvis is greatly contracted, necessitating Caesarean section for delivery

The thorax may be markedly distorted and compressed laterally with an increase in the anterior posterior diameter and protrusion of the sternum pigeon breast The clavicles become arched The skull is not deformed

The long bones become irregularly bowed with the legs affected more than the arms Genu valgum is common The cortex of the bones is thin the trabeculae sparse and fragile and the marrow spaces greatly enlarged The outer surface of the bones is injected and uneven with echymotic areas evident on cross section The periosteum is hyperemic and thickened and adherent to the new uncalcified osteoid tissue which is deposited beneath it

Microscopically one observes a deficient calcification of the bones The osteoclasts are normal but the osteoblasts appear in abnormal abundance[16] This histological picture is in contrast to that seen in Paget s disease or in hyperparathyroidism and distinguishes it from these conditions

Except for the changes in the bones there are but few pathological changes of importance elsewhere in the body The epiphyses and joints are normal except for secondary changes following disuse when ankylosis may result The costo chondral junctions in extreme cases may become hypertrophic with erosion of the cartilage by the vascular marrow as in infantile rickets The muscles frequently are atrophic as a result of disuse Compensatory enlargement of the parathyroids occurs

X Ray Findings

The x ray appearance of the bones in osteomalacia is characteristic There is evidence of marked rarefaction of the bones which appear as hazy, indistinct shadows without the normal contrast to the soft tissues surrounding them The bony trabeculae are sparse or absent the cortex is thinned and the marrow cavity greatly dilated The epiphyses are unusually transparent but otherwise normal in appearance[6]

In advanced cases the deformities of the pelvis and thorax as already described are evident The vertebrae show compression and distortion with lateral contraction and the concave cupping of the articular surfaces which has been designated as fish vertebrae Fractures when they do occur, tend to be without displacement and show little or no callus formation Pseudofractures first described by Looser are observed commonly in the roentgenogram[19] Deformities of the pelvis and thorax described in the preceding section, are observed

Biochemical Considerations

The patient with osteomalacia manifests a negative calcium and phosphorus balance with an increased excretion of these elements in the feces and a decreased excretion in the urine In severe cases of the disease this negative calcium and phosphorus balance may persist even when the calcium and phosphorus intake in the diet is high and is only remedied by administration of vitamin D which increases the absorption and utilization of these mineral elements[11]

In milder cases the calcium level of the blood serum may be normal the inorganic phosphate only slightly reduced and the phosphatase level of the blood serum only slightly elevated In severe cases however the blood serum calcium and inorganic phosphate are decreased and the phosphatase is moderately elevated[7 8] The serum calcium usually ranges from 8 to 9 mgm per 100 c c compared to 9 5 to 11 in the normal the inorganic phosphorus from 2 to 3 instead of 5 to 3 5 mgm as in the normal and the phosphatase activity from 10 to 25 Bodansky units compared to 4 in the normal As healing progresses normal values are restored in all of these functions

As a result of the mineral deficiency in the bones their calcium and phosphorus content is reduced the former relatively more than the latter Hence the calcium phosphorus ratio is decreased The magnesium content of the bones is increased possibly as a compensation for the reduced calcium The sulfur content of the bones is increased as a result of the increased formation of organic osteoid tissue[17]

Quantitative measurements of the calcium and phosphorus metabolism in osteomalacia during pregnancy have been carried out by Liu and his co workers[1] They have demonstrated that the metabolic behavior of these patients is entirely normal On an adequate vitamin D and a moderately high calcium and phosphorus intake the patient with osteomalacia has no difficulty in retaining enough calcium and phosphorus for the needs of gestation and may in fact replenish partially the depleted maternal stores of these elements Osteomalacia thus involves no fundamental metabolic disorder but on the other hand it is a purely deficiency disease

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Symptoms

The symptoms of osteomalacia are gradual and irregular in onset which may render the diagnosis difficult in early stages of the disease [1] The disease tends also to spontaneous remissions particularly during summer months when the patient is more likely to have access to the sunlight In its mildest form the principal symptoms are weakness and dull rheumatic pains in the pelvis, legs, back, hips or knees The pains are deep seated and may have a sacro iliac distribution Undoubtedly the condition in many patients with these milder manifestations of the disease is not recognized unless roentgenological studies are made [1]

In the more advanced forms of the disease the pain in the back and extremities may become excruciating The pain tends to be aggravated on standing and is more acute at night Girdle pains may be noted The bones are sensitive to pressure Muscle weakness may be marked The muscles of the legs, particularly the abductors and flexors of the hips and knees, are held rigidly and are straightened with difficulty

The gait assumes a peculiar shuffle 'duck gait', in which the advancing leg is held stiffly while the other is dragged forward without raising it from the ground Ultimately locomotion becomes impossible, the patient lying with the knees drawn up and movement of the lower joints is limited and painful Wasting of the muscles exaggeration of the reflexes, ankylosis and distortion of the joints disturbances of sensation, an intention tremor and even paralysis may be present at this advanced stage of the disease (Fig 14)

In long standing osteomalacia with hypocalcemia manifest tetany, cramps in the muscles dental caries[14] and cataracts[13] may be noted Latent tetany may be present and the signs associated with this condition Chvostek's sign, carpopedal spasm Trousseau s phenomenon and Erb s sign may be elicitable

Except in the very late stages of the disease when deformities of the chest may lead to dyspnea there are few symptoms other than those already noted Menstruation usually is normal except in cases secondary to steatorrhea when amenorrhea has been noted Before the advent of modern therapy the course of the disease was prolonged for 6 to 30 years with frequent remissions in its course In the final stages of the disease secondary infections, cachexia and other complications terminated the clinical picture

Diagnosis

Generalized decalcification of the skeleton may occur in a number of conditions[9] but the osteoporosis so produced should not be confused with osteomalacia which is a specific deficiency disease in which rarefaction of the bones is also an



FIG 14—Osteomalacia girl age 15 (Case of Dr C F Painter)

important feature There is a fundamental difference between osteoporosis and osteomalacia[1] In the former there is a failure of the osteoblasts to lay down a sufficient osseous matrix as a result of which the bones become rarefied Osteoporosis is not a disorder of calcium metabolism but an atrophy of the osseous matrix Hence the blood calcium phosphate and phosphatase levels usually are normal In osteomalacia on the other hand osteoblastic activity is normal or increased There is ample formation of osteoid matrix which however remains uncalcified

Osteoporosis is encountered in a number of clinical conditions hyperparathyroidism senescence following the menopause Cushing s syndrome hyperthyroidism multiple myeloma osteonephropathy and as a result of disuse These conditions can however usually be readily differentiated from osteomalacia

Hyperparathyroidism is distinguished by the chemical findings in the blood high calcium low phosphate elevated phosphatase activity Senile osteoporosis is most marked in the spine resulting in thoracic kyphosis which is encountered in older individuals and the serum calcium phosphate and phosphatase levels are normal In post menopausal osteoporosis the osteoporosis is also most marked in the spine

In Cushing s syndrome the presence of obesity hypertension and purplish striae usually aid in diagnosis The osteoporosis in this condition usually is most marked in the spine and the skull is involved most often with irregularly distributed areas[33] The chemical findings in the blood are normal In hyperthyroidism the osteoporosis is generalized and homogeneous the serum calcium and phosphate normal and the serum phosphatase slightly elevated The evidence of increased metabolic activity and other symptoms due to hyperthyroidism render the diagnosis evident

In multiple myeloma the osteoporosis rarely is generalized or homogeneous the calcium phosphate and protein levels of the blood may be elevated and Bence Jones protein is present in the urine in over two thirds of the cases The first symptoms frequently are in the ribs Pain and tenderness are cardinal symptoms as they are also in osteomalacia

In osteoporosis due to disuse e g following the application of a cast the skull is seldom affected There is a flaccid rather than the spastic muscular contractions observed in osteomalacia The phosphatase activity remains normal or low In renal osteonephropathy and skeletal changes and the deformities are unlike those which are seen in osteomalacia The evidence of renal disease and the presence of hyperphosphatemia also readily differentiate this group of conditions

The history of an inadequate calcium and vitamin intake of repeated pregnancies with prolonged lactation or of chronic diarrhea or steatorrhea together with the nature of the pain usually suggests the diagnosis of osteomalacia

TREATMENT

Before the recognition of osteomalacia as a deficiency disease patients were subjected to oophorectomy or treated with epinephrine, phosphorus and other medicament At present prompt and satisfactory results are obtained by the administration of a high calcium and phosphate diet with the addition of ample amounts of vitamin D Where the diet is not too low in calcium, the administration of vitamin D alone proves curative Administration of milk (1½ quarts daily) with 8 c c of codliver oil (12 U S Pharmacopoiea or international units) daily will suffice to ameliorate the condition Calcium phosphate may be administered also in the form of calcium glycerophosphate 12 to 25 c c daily, or in the form of dicalcium phosphate

Since in most instances calcium rather than phosphate is deficient[3], the addition of salts of the former alone to the diet suffices Calcium may be administered most cheaply in the form of calcium chloride The unpalatable taste of this salt may be masked by prescribing it as a 25 per cent solution in syrup of licorice in doses of 8 c c, three or four times daily Calcium may be administered also in the form of calcium lactate in doses of 8 to 12 gm daily

Vitamin D may be supplied as codliver oil, 8 to 15 c c of the U S Pharmacopoiea potency daily in the form of other fish oils or as crystalline vitamin D, calciferol or crystalline vitamin D_3 One milligram of calciferol is equivalent to 40,000 international or U S Pharmacopoiea units of vitamin D

In patients in whom steatorrhea or chronic diarrhea is the primary condition responsible for the development of osteomalacia treatment directed to overcoming the primary condition obviously is indicated The addition of bile salts[3] is advocated in these cases to aid in the absorption of fat or fat soluble vitamin D Any condition interfering with the absorption of fats may prevent adequate absorption even with a large intake of this vitamin

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Treatment

Before the recognition of osteomalacia as a deficiency disease patients were subjected to oophorectomy or treated with epinephrine phosphorus and other medicaments. At present prompt and satisfactory results are obtained by the administration of a high calcium and phosphate diet with the addition of ample amounts of vitamin D. Where the diet is not too low in calcium, the administration of vitamin D alone proves curative. Administration of milk (1½ quarts daily) with 8 c c of codliver oil (1? U S Pharmacopoeia or international units) daily will sufice to ameliorate the condition. Calcium phosphate may be administered also in the form of calcium glycerophosphate, 12 to 25 c c daily, or in the form of dicalcium phosphate.

Since in most instances calcium rather than phosphate is deficient[1], the addition of salts of the former alone to the diet suffices. Calcium may be administered most cheaply in the form of calcium chloride. The unpalatable taste of this salt may be masked by prescribing it as a 25 per cent solution in syrup of licorice in doses of 8 c c three or four times daily. Calcium may be administered also in the form of calcium lactate in doses of 8 to 12 gm daily.

Vitamin D may be supplied as codliver oil, 8 to 15 c c of the U S Pharmacopoiea potency, daily in the form of other fish oils or as crystalline vitamin D, calciferol or crystalline vitamin D_3. One milligram of calciferol is equivalent to 40 000 international or U S Pharmacopoiea units of vitamin D.

In patients in whom steatorrhea or chronic diarrhea is the primary condition responsible for the development of osteomalacia, treatment directed to overcoming the primary condition obviously is indicated. The addition of bile salts[3] is advocated in these cases to aid in the absorption of fat or fat soluble vitamin D. Any condition interfering with the absorption of fats may prevent adequate absorption, even with a large intake of this vitamin.

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PART VI

DYSCHONDROPLASIA
(*Hereditary Deforming Chondrodysplasia*)

INTRODUCTION

Classification — There are a number of disorders of endochondral ossification resulting in alterations of skeletal growth The nosology of this diverse group of developmental disorders still is obscure There has been a tendency to designate each new variation observed by a new name or eponym the result of which has been complete confusion In general we may differentiate the following groups of disorders involving an abnormality of the epiphyseal cartilage itself or of the process of endochondral ossification

I Achondroplasia or chondrodystrophia fetalis a well defined clinical entity discussed in the following section of this chapter in which the growth cartilage is defective or undergoes degeneration in early fetal life

II Dyschondroplasia the subject of the present section which includes a number of allied conditions involving an abnormality in the process of endochondral ossification

III The osteochondroses This group includes the so called osteochondritides in which there is an aseptic necrosis of the epiphyseal cartilage and disorders in which there is a disturbance in endochondral ossification The former group includes Calve Legg Perthe s disease or coxa plana when the process involves the head of the femur Osgood Schlatter s disease when involving the tibial tubercle Koehler s or Freiberg s disease when involving the scaphoid tarsal or second metatarsal bones Scheuermann s disease when involving the vertebral epiphyses Kienbock s disease when involving the lunate bone

Among the osteochondroses are included also the condition designated by Barber[4] as osteochondrosis deformans tibiae or non rachitic bow leg in children This condition is due to a disturbance in enchondral ossification resulting in metaphyseal deformity with deformation frequently of the epiphysis[5 6] There is a retardation of the normal transformation of primordial cartilage into growing bone resulting in an irregularity of ossification at the epiphyseal metaphyseal junction

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of the long bones[1] The condition may thus be looked upon as a dyschondroplasia related to Morquio s disease

IV Morquio s disease or osteochondrodystrophia deformans is discussed in Chapter V of Volume V of the Oxford Medicine In this disease there is also a disordered epiphyseal development[4] with absence frequently of the heads of the femora, dwarfism deformity of the spine and crippling

In addition to the above described varieties of recognized disorders cases have been reported which do not fall into any clear cut designation[6,18,3] For example certain atypical forms of chondrodystrophy appear to be intermediate between Morquio s disease and achondroplasia[56,6] Further study may perhaps indicate a closer fundamental relationship between certain of these disorders

In the present section we shall consider a fairly definite clinical group of disorders which, although manifesting themselves in several varieties, appear to represent a single fundamental disorder, which may be designated simply as dyschondroplasia

Definition — An hereditary congenital abnormality of osteochondral development resulting in irregularity and arrest in growth at the metaphyseal ends of the long bones with expansion at their ends secondary deformity, the occurrence of multiple cartilaginous masses (enchondromas) and osteocartilaginous masses (exostoses) and defects in the normal architecture of the bone

Synonyms — The condition has been designated by a variety of names in an attempt to emphasize some particular manifestation of the disorder and under the mistaken view that the different varieties represented distinct clinical entities The more commonly used designations are hereditary deforming chondrodysplasia Ollier s disease multiple cartilaginous exostoses hereditary multiple exostoses chondral or exostotic dysplasia multiple congenital osteochondromata diaphyseal aclasis multiple cancellous osteomata multiple chondro osteomata, dystrophia ossea congenita exostosis multiplex cartilaginea skeletal enchondromatosis eccentro osteochondrodysplasia chondral dysplasia ossified diathesis, osteocartilaginous exostoses

The terms hereditary deforming chondrodysplasia " and " multiple cartilaginous exostoses have been used most widely The term *dyschondroplasia* has been adopted for this section because it includes not only the above mentioned disease but also Ollier s disease and other varieties of disorder which comprise a single clinical entity Ollier[18] in 1899 introduced the term, dyschondroplasia to designate what since then many have erroneously considered to be a distinct clinical entity

Historical — Instances of dyschondroplasia characterized by multiple bony prominences have been noted from earliest times as interesting anomalies The first recorded instance in modern literature appeared in 1825 in a Guy s Hospital

Report [9] In 1837 Caesar Hawkins[1] described a typical case and designated the condition as laminated exostoses Gibney in 1875 reported the first case in the American literature Stanley is quoted by Reinecke[6] as having first noted the familial tendency of the disorder in 1849

In 1898 Ollier[4] first called attention to a condition in which incomplete areas of ossification of the metaphyses with clear areas in the juxta epiphyseal portions of the long bones due to the presence of islets of cartilage were associated with multiple exostoses He designated the condition as dyschondroplasia recognizing the similarity of the condition to the previously reported osteogenic exostoses However he as well as Molin[4] who published a dissertation on the subject in 1900 emphasized the unilateral nature of the disorder in spite of the fact that certain of Ollier s original cases were bilateral Although many subsequent authors have considered Ollier s disease as a clinical entity separate from multiple exostoses it is now clear that the condition is only one variety of dyschondroplasia and that unilateral involvement is neither an essential nor frequent occurrence although asymmetrical involvement is not uncommon[13]

Incidence — Dyschondroplasia is not a rare condition Reinecke [9] in 1891 collected 172 cases occurring in 36 families

Frangenheim [4] in 1912 published an exhaustive and critical review of the subject In 1915 Ehrenfried [1] reviewed 300 articles from which he was able to collect 600 cases from the literature adding 99 from the American literature in 1917 Hale in 1930 collected 50 additional cases from the literature and Bromer and John[10] reported 11 more in the following year There have been numerous reports of additional cases in the recent literature the Vanzants for example reporting 36 instances of the disease in 5 generations of 78 members

ETIOLOGY

The etiology of the disease still is obscure Earlier theories which attributed the disorder to infections rickets or endocrine dysfunction have been discarded Von Bergmann first suggested that the disease results from a disturbance in development of the intermediary cartilage due to a defective anlage Jansen considered the disease to be due to a failure of the normal osteogenic processes particularly a retardation in tubulation cell division and differentiation of the bone Keith points out that in the normal process of osteogenesis the newly deposited bone in the epiphyseal cartilage is resorbed reshaped and remodeled to form a narrow metaphysis As a result of a failure of this process the diaphyseal cartilage is exposed and expands in abnormal directions

Hale believed the process to be the result of an impression on the germ plasm consequent to recurrent fractures Such a view is however not in accord

of the long bones[31] The condition may thus be looked upon as a dyschondroplasia related to Morquio s disease

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Historical —Instances of dyschondroplasia characterized by multiple bony prominences have been noted from earliest times as interesting anomalies The first recorded instance in modern literature appeared in 1825 in a Guy s Hospital

Heredity — The hereditary nature of the disease is well established[44 57 59 63] Ehrenfried[1] found a familial tendency in 83 per cent of his cases Reinecke[1] found multiple exostoses in 3 4 and 5 generations of the 30 families which he investigated Percy traced a family with exostoses through four generations in whom 27 per cent of all persons were affected In the genealogy presented by Vanzant 36 persons in five generations of a family of 78 members were afflicted an incidence of 46 per cent In this family the union of two cousins one of whom had the disease and possibly also the other, resulted in seven offspring all of whom were afflicted

It must be remembered that the disease often is mild particularly in the female and hence unless careful roentgenological studies are made of all members of an affected family one cannot determine accurately the exact incidence of the disease since the presence of smaller lesions will be missed completely in an examination of the patient not accompanied by x ray study

The disease appears to have a recessive tendency in the female and hence may be transmitted through an apparently unaffected female The inheritance usually is direct but the particular form in which the disease manifests itself that is as exostoses or as enchondromas, may differ from parent to offspring and also among siblings in a given family[5]

Pathology

The fundamental disturbance in endochondral ossification may give rise to a variety of abnormalities which differ so profoundly in their superficial manifestations as to suggest the existence of a variety of separate clinical entities It is now evident however, that these varieties represent a single primary disorder Although many intermediate forms are encountered the following represent the principal manifestations in dyschondroplasia

1 Enchondromas in which outgrowths of cartilage which may be partially ossified osteochondromas are predominant The presence of these cartilaginous masses particularly when predominantly unilateral in distribution constitute the variety of dyschondroplasia usually referred to as Ollier s disease The enchondromas may be limited to islands of cartilage cells within the epiphyses or shaft or may constitute cartilaginous masses protruding at the metaphyseal junction of the bone[16]

2 Multiple cartilaginous exostoses which are the predominant manifestation of the condition designated by Ehrenfried[1] as hereditary deforming chondrodysplasia This group is characterized by bony outgrowths in the form of knobs spurs or pedunculated masses which appear as multiple exostoses on the diaphysis of the long bones near the epiphyseal lines

with modern principles of genetics Bentzon[5] attempted to reproduce the lesions of dyschondroplasia by injecting the sympathetic nerves with alcohol He believed the disorder to result from hyperemia secondary to paralysis of the sympathetic nervous control of the nutrient artery Jansen[37], on the other hand believed the disease to be a result of vasoconstriction due to overstimulation of the sympathetic nerves Jacobson[36] also favors the view that the failure of absorption of the cartilage growth plate of the epiphysis is induced by an abnormality of blood supply or nervous control

Speiser[9] on the basis of a careful postmortem study, suggested that dyschondroplasia results from an abnormal metaplastic activity of the periosteum which begins between the fourth and fifth months of fetal life Hume[34] also attributes the disorder to an abnormal growth of the epiphyseal disc with failure of the subperiosteal bone to maintain this accelerated growth

Geschickter and Copeland[6] have discussed at length their views as to the pathogenesis of dyschondroplasia and its relation to other benign tumors of bone They attribute the formation of both isolated and multiple osteochondromas to a defect in the periosteum which leads to persistence of the perichondrium and the precartilaginous connective tissue As pointed out by Vanzant[60] this theory fails to account for the existence of those rare lesions occurring in the bones of the skull which arise from primitive membrane without the intermediation of cartilage

Age — The disease being the result of an abnormality in growth is rarely evident at birth It begins during infancy but usually remains unrecognized until later childhood unless discovered incidentally by x ray Honeij[33] cites the ages at which medical attention was sought by 27 patients as follows, 1 at birth, 12 before the age of 5 7 between the ages of 5 and 10 4 between the ages of 10 and 15 2 between the ages of 15 and 20 and 1 after the age of 20 Milder forms of the disease are encountered often during x ray examinations in adults, but the superficially manifest exostoses or deformities usually will become evident in early childhood With cessation of rapid growth at puberty the process tends to become quiescent

Sex — The disease is more common in the males of affected families than among the females it being usually stated that there is a ratio of 3 1 in the incidence in the two sexes Ehrenfried[1] found a ratio of 5 2 Percy[49] in 30 members of a single family found a ratio of 5 1 while in Vanzant's[60] series, including 455 persons the ratio was approximately 1 5 1 This difference in the incidence of the disease in the two sexes is due to the fact that the disorder tends to be less severe and hence often remains unnoticed in the female Like baldness the disease apparently is inherited through both sexes but has a recessive tendency in the female

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3 Changes in the architecture of the bone which may be manifested in a variety of ways Voorhoeve [1] described longitudinal striations in the metaphysis of the long bones pelvis and other affected bones These striae, evident in the roentgenogram are due to areas of rarefaction Albers Schonberg[1] in 1915 reported a case in which in addition to the above mentioned striae, translucent spots due to dense areas of bone were present in the metaphyses of the femora The fine mottling of the skull described by *Mahorner[43] also is probably a manifestation of irregular calcification occurring in the disease*

The three types of abnormalities just described merely represent three groups of manifestations of dyschondroplasia Many instances are recorded in which *for example, the striations and dense areas described by Voorhoeve[61] and Albers* Schonberg[1] were present with the exostoses and enchondromas usually associated with the more classical forms of the disorder [17] In the same family one may encounter individuals in whom either exostoses or enchondromata predominate[38] It should be emphasized that exostoses need not invariably be present, for diaphyseal changes alone as in the cases of Voorhoeve and Albers Schonberg may be encountered These may represent, as Alley suggests, a preexostotic, latent or mild form of the disease

A failure to appreciate the different forms in which dyschondroplasia may manifest itself is responsible for the number of cases reported as atypical or as examples of new diseases

Since the disorder is a disturbance in the proliferation and ossification of the intermediate cartilage during the period of growth the lesions are most striking and frequent at sites of rapid bone growth namely at the knee ankle hip and wrist The skull pelvis ribs and spine may be affected also but these are affected less commonly and may show merely the changes in architectural structure described above The small bones of the wrist and ankle are frequently the site of *enchondromata which may be huge and deforming[1]*

The changes in the metaphysis are the most characteristic feature of the disorder The metaphyseal ends of the bones are expanded in the shape of a trumpet with a distinctive squaring of the end of the bone This change is seen most often in the femur, tibia fibula ulna and radius *A cyst like enlargement of the distal* end of these bones may occur

Exostoses are the most striking features of the disease (Fig 15) They may be few in number, but in some cases over a hundred tumors may be evident during life[3] These exostoses usually are symmetrical but in some instances are predominantly unilateral in distribution In such cases careful examination by x ray may reveal changes of minor degree in the opposite side of the body The bony outgrowths may occur in the shape of spurs knobs cauliflower like excrescences or as pedunculated masses pointing away from the joint

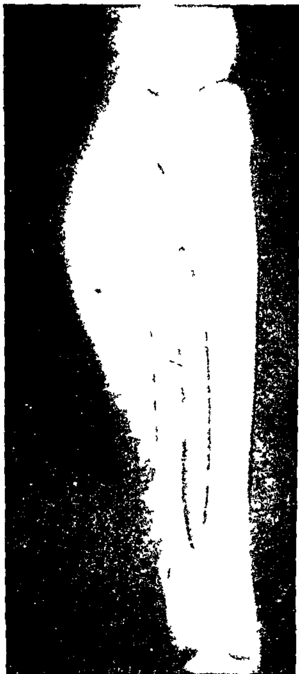


FIG 15 —Dyschondroplasia (hereditary deforming chondrodysplasia) male age 19 years X ray of lower leg showing large exostosis at upper end of fibula and synostosis between fibula and tibia in their lower portion (Case of Dr A Ehrenfried)

The disturbance in endochondral growth results in shortening of the long bones Bony fusion may occur between the lower ends of the tibia and fibula or the ulna and radius (Fig 15) Due to the arrest in growth of only one of these pairs of bones the other member tends to become bowed Deformities dislocations spiral twisting of the shaft and ulnar displacement of the wrist club hand, are common The epiphyseal cartilage often is thin and irregular in outline In some instances it is prematurely calcified It is this interference with normal activity of the epiphysis which results in dwarfism in cases severely affected with the disease In the three cases described by Dwyer[7] there was marked involvement of the epiphyseal cartilage not unlike that seen in osteochondritis deformans juvenalis and showing some of the characteristics of chondrodystrophia fetalis

Except for the presence of islands of cartilage translucent areas striae and mottling the diaphyses of the bones are normal Most of the exostoses are found in the cortical region of the bone However there may also be an inward growth of bone with the formation of central chondromas It is the union of two such contiguous cartilaginous growths which gives the characteristic synarthrosis of *the fibula and tibia or ulna and radius*

Microscopically the epiphyseal cartilage is found to be greatly disordered with evidence of overgrowth Throughout the zone of proliferation are noted masses of cartilage cells in disorderly arrangement and usually incompletely calcified These irregular masses of cartilage may appear also farther along the shaft of the bones being displaced into the diaphyses as growth continues

The exostoses appear at the end of the bones as masses of bone surrounded by a layer of dense cartilage which in turn is encased in a layer of cells which represent the precartilaginous connective tissue True enchondromas some of which may be partly ossified osteochondromas may be associated with the exostoses or occur alone The epiphysis like architecture of the cartilaginous exostoses is a result according to the experimental studies of Jacobson[34], of the mutual polarity existing when bone and cartilage are growing together

Symptomatology

The disease usually shows no primary symptoms the patient seeking attention only when tumors and deformities become evident These are only rarely evident at birth or during infancy becoming prominent usually between the ages of five and twelve Irregular nodules in the region of the epiphysis of the long bones frequently are the first manifestations of the disease These tend to grow slowly during the period of skeletal growth The most common sites involved are the juxta epiphyseal lower ends of the radius and ulna upper end of the humerus lower end of the tibia and fibula and the region of the elbow joints They may

occur also in the ribs posteriorly near the tuberosities in the phalanges and rarely in the innominate bone the skull and spine

Pain or tenderness over the tumors never occurs except as a result of trauma Since the exostoses tend to point away from the joint there is usually no interference with movement unless synostosis and deformity are present

The deformities most commonly encountered are large exostoses or osteochondromas at the joints of the knee elbow or wrist Bowing of the tibia may lead to pes valgus and bowing of the radius to club hand (Fig 16) The deformities usually are symmetrical but may be predominantly unilateral Mechanical limitation of the hips or ankles also is frequent[39] Dwarfism of a moderate degree is a common stigma of families affected by the disorder, the diminution in height being generally confined to the lower extremities The central point of the body, however is only elevated two to four centimeters above the symphysis and thus is never marked as in achondroplasia

As is the case in other congenital bone diseases, e g fragilitas ossium or fibrous dysplasia of bone the bony changes may be accompanied by vascular abnormalities Carleton Elkington Greenfield and Robb Smith[1] recently have collected 18 examples of dyschondroplasia associated with vascular hamartomata cavernous angiomata and phlebectasia They designate the condition as *Maffucci's syndrome* Massive enchondromata of the metacarpals are striking features of some of the cases in whom this condition occurs

Metabolic studies have revealed no abnormalities either in the composition of the blood or in the metabolism of calcium or phosphorus °

X RAY FINDINGS

The x ray reveals the characteristic findings in the disease and is necessary for establishing the diagnosis in cases where deformities and exostoses are not superficially evident or absent [3, 41] The salient features of the disease are the presence of multiple exostoses and osteochondromas widening of the metaphyseal ends of the long bones and the deformities striae mottling and areas of increased density described in preceding sections

The appearance of the tumors is variable depending on the relative amount of cartilage and bone present Some are extremely dense while others appear as a cluster of cyst like enlargements at the end of the bone The bone may appear mottled with areas of decreased density due to irregular calcification in the region contiguous to the tumor The synarthrosis at the joints of the wrist and ankle with one bone arched as in a bow and the other shortened is characteristic The fingers and toes may show justa epiphyseal enlargements with variations in their length



FIG 16—Dyschondroplasia (hereditary deforming chondrodysplasia) male age 20 years X ray of forearm and hand showing shortening of ulna with characteristic deformity of distal end and bowing of the radius note the ulnar deviation of the hand

Although the bones of the head of the face and of the vertebral column are affected infrequently, they may show exostoses, irregular areas of calcification and deformity

Complications

Complications are rare and are due for the most part to deformities The exostoses may impinge on nerves or contiguous structures and give pain dysfunction of the limb paraplegias and local paralyses Fractures occur rarely Compression of the cord brain and pelvic organs may occur[7, 6] The first named may lead to paralysis the second to epilepsy, apoplexy and defective hearing and the last to dystocia

The most serious complication results from the tumor becoming malignant This occurs probably in less than 5 per cent of the cases but should be suspected always when a tumor in an adult suddenly begins to increase rapidly in size[6]

Course and Prognosis

The exostoses usually cease growing at maturity remaining stationary in size in the adult In some instances retrogression of the exostoses has been noted At times however growth may continue for many years

Except in the cases where sarcomatous changes occur or the other unusual complications supervene the general health is unaffected and the life expectancy is not shortened[3]

Diagnosis

The occurrence of multiple cartilaginous exostoses the typical x ray findings and the history of other members of the family being affected similarly usually leaves little doubt as to the correct diagnosis Differentiation is made readily from benign and malignant neoplasms, traumatic exostoses multiple myeloma rickets tuberculosis syphilitic and infectious osteomyelitis and periostitis

The expanded metaphyses multiple nature of the tumors situated at the diaphyseal end of the metaphysis the characteristic fusion of the ulna and radius or tibia and fibula leave no question as to the diagnosis in the typical case However atypical cases and particularly where no family history of the disorder is obtainable may present a problem in diagnosis The absence of exostoses particularly in the female requires careful roentgenographic study for evidence of the other characteristic findings striae mottling areas of condensation

Morquio s disease is differentiated by the early cessation of growth the flattening of the vertebral bodies the severe kyphosis and crippling and the great short

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18 DALE T Unusual forms of familial osteochondrodystrophy Acta radiol 1931 XII 337

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36 JACOBSON S A Contribution to patho enesis of multiple hereditary osteochondromatosis experimental study Am Jour Cancer 1940 XXXIX 2 0

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ening of both trunk and extremities Chondrodystrophy usually is recognized by the characteristic appearance of the face and hands and the extreme micromelia

Treatment

Surgical removal of tumors may be required where these are large and give symptoms due to pressure on nerve trunks or interference with movement at the joints To avoid recurrence the dissection of the surrounding tissues should be extracapsular[8, 11, 13] Osteotomy is indicated in cases of varus or valgus deformities Other orthopedic measures such as the use of mechanical aids, may be helpful also

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Part VII

CHONDRODYSTROPHIA FOETALIS
(*Achondroplasia*)

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Revised by ARTHUR GROLLMAN

Introduction

Definition — Achondroplasia is a relatively rare congenital disease of the skeleton affecting only those bones formed from cartilage and invariably beginning in early fetal life The characteristic features of the disease at birth are a moderately enlarged head depression of the root of the nose, trident hands and remarkably short and curved extremities micromelia due to arrested development of the long bones which contrast sharply with the normally developed trunk In the few patients who survive these characteristics become more accentuated and produce a type of dwarfism

Synonyms — Rachitis micromelica achondroplasia micromelia chondromalacia chondritis foetalis pseudochondritis chondrodystrophia foetalis (hyperplastica hypoplastica, malacica) micromelia micromelia achondrodystrophica diaphyseal aclasis

In earlier writings the disease often was classified under the term osteogenesis imperfecta or designated as osteopsathyrosis with periosteal aplasia Some mistook the condition for a form of cretinism and designated it as cretinoid dysplasia

In France the name achondroplasia has come to be used almost universally while in Germany the term chondrodystrophia foetalis is employed more commonly The latter implying a developmental disorder of the cartilage in fetal life is more accurate than the former which signifies an entire absence of the normal activity of the cartilage in producing osseus tissue which is not strictly the case in this disease Achondroplasia has the advantage however, of priority and common use

Historical — Unmistakable examples of this disease are recorded in medical writings for considerably more than a century, and examples of the condition are

found in the art of medieval and ancient times[4, 31, 37] The first case was described by Sommering in 1791 his report of the autopsy findings in the case of a deformed fetus making it clear that he was dealing with a typical example of this disease

Romberg[35] (1817) Weber[46] (1829) and Busch[5] (1836) each recorded a case showing the salient features of achondroplasia In each instance the author regarded the condition as fetal rickets In 1856 Virchow[43] reported the first pathological studies of such a case also classifying the condition as fetal rickets A few years later H Muller[7] (1860) made an exhaustive study of several cases of the disease and showed that the disease was distinct from the ordinary form of rickets as seen in children He differentiated a congenital form of rickets as exemplified by these cases Muller was the first to recognize the synostosis of the early bone centers at the base of the skull and to attribute the bone changes to a disease of the primordial cartilage This important work marks the real beginning of our present knowledge of the disease The same conclusions were reached by Winckler (1871) and Urtel[4] (1873) from histological studies of a similar fetus the former author suggesting the term Rachitis mit Micromelia Parrot[3] (1878) separated the condition entirely from rickets congenital syphilis and cretinism and suggested the term achondroplasia He defined the main process as a dystrophy of the primordial cartilage accompanying the first osteogenetic growth in the fetus

The most important single contribution to the pathology of the disease was made by Kaufmann in 1892 He advocated the name *chondrodystrophia foetalis* This author on a pathological basis and as a result of most careful study of 14 cases described three forms as follows (1) chondrodystrophia hypoplastica in which the cartilage proliferation is diminished and the outward appearance of the epiphysis does not seem changed (2) chondrodystrophia malacica or chondromalacia foetalis characterized by a softening and breaking down of the epiphyseal cartilage (3) chondrodystrophia hyperplastica due to an undisciplined growth of the epiphyseal cartilage which is vascular and soft The growth of the epiphysis produces a marked enlargement in the region of the joints The bones are harder than in the other two forms chondrodystrophia hypoplastica and chondrodystrophia malacica and more prone to fractures

A remarkably complete and accurate description of the clinical features of achondroplasia was published by Marie[6] in 1900 Many important contributions have been made to the subject in recent years particularly as regards the pathogenesis and hereditary nature of the disease[2, 9, 2, 4] It is impossible to make any exact statement regarding the incidence of achondroplasia Notwithstanding the fact that it is the most common of the congenital bone affections it must be considered as relatively rare

Etiology

Heredity is fully established as the etiological factor in the development of the disorder Many cases are on record in which achondroplastic dwarfs have occurred in three or more successive generations [16] In the frequently quoted case of Porter there were six typical examples of achondroplastic dwarfs in three generations

A number of theories attempted to explain the pathogenesis of the disease on the basis of some assumed endocrine or developmental disorder Jansen[17] attributed the disease to an increased hydrostatic pressure with infolding of the amnion during early embryonic life but this view which formerly received much attention is no longer tenable[4] Achondroplasia apparently is due to some congenital defect in the germ plasm which is inherited dominantly according to the Mendelian law of inheritance [8] It appears apparently with relative frequency by mutation Advancing maternal age seems to play a definite role in causing the disease

For a further discussion of the etiology of the disorder the reader is referred to the article on Dwarfism in Vol III Chapt XIX of Oxford Medicine

Pathology

In consequence of the fact that achondroplasia usually runs a fatal course i e the individual dying in utero or soon after birth abundant opportunity for pathological studies has existed and the literature is especially rich in pathological reports[1 3d] beginning with that of Virchow[43] in 1856

General Deformities

The general appearance of the fetus with this affection is striking and entirely distinct from that seen in any other disease [9] A diagnosis can be made readily on inspection The infant usually is plump and the thickened skin is thrown into folds especially about the joints an appearance which Weber[48] describes as a dwarf with much too large clothes A disproportionately large head and normally developed trunk contrast sharply with the very short but usually well formed extremities As a result of the micromelia or phacomelia the stature is much abbreviated

The depression of the root of the nose gives it a peculiar saddle form or pug nose appearance The prominent lower jaw prognathus thick lips and protruding tongue suggest cretinism A marked prominence of the abdomen is the rule Throughout the body the changes are symmetrical[19 9]

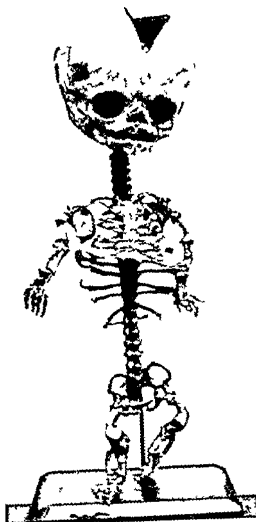


Fig 17 —Chondrodystrophia foetalis (achondroplasia) Skeleton of seven months foetus (Warren Museum Harvard Medical School)

Individual Deformities

In the normal infant the central point of the body is at the navel but in the achondroplast the disproportion between the legs and trunk raises the point to the xyphoid cartilage Instead of the average normal length 50 cm the achondroplastic infant measures from 30 to 40 cm and a few are recorded considerably under 30 cm

The head shows a varying *degree of enlargement and may be hydrocephalic (Fig 17) but in most cases* the microcephaly is more apparent than real The skull is not strikingly changed in shape except for a considerable prominence of the frontal region and a tendency to the brachycephalic type In contrast to the condition found in fragilitas ossium the cranial bones are well formed and hard and the fontanelle and sutures normal or prematurely closed

The bones of *the skull base are formed largely from cartilage hence like the* long bones they play a prominent part in the achondroplastic process The changes are exceedingly variable some parts being normal while others are abnormal Premature union of the bones and arrest of development are the two most important conditions found

The *os tribasilaris* at the time of birth is composed of three separate parts *the basilar portion of the occipital bone and the two portions of the sphenoid* which are united by synchondrosis The synchondrosis between the two sphenoids normally ossifies soon after birth but the synchondrosis between the occipital and the sphenoid bones does not become bony until adult life These bones often are firmly united at birth in the achondroplastic fetus and it is this premature synostosis which is *largely responsible* for the retardation *in the growth of the basis cranii and the resulting deformities* Likewise *the bony union of the* four bones surrounding the foramen magnum should not occur until about the sixth year but in this disease usually they are completely synostosed at birth

The vertebral column rarely escapes involvement but the alterations usually are not very noticeable The vertebrae are wedge shaped giving rise to thoracico lumbar kyphosis [7]

The changes in the thorax are never striking nevertheless alterations indicating arrested development in the ribs do occur The thorax sometimes is small above and broadened below A projecting sternum and flattening of the chest have been observed Several authors have described a well marked rosary similar *to the rachitic rosary but the enlargement at the junction of the* cartilage and ribs is not as is the case in rickets due to cartilage proliferation but *to bone overgrowth* from the epiphyseal cartilage of the rib This thickening is more marked on the inner thoracic wall than the outer The clavicle and scapula usually escape noteworthy changes except that they are apt to be somewhat below the nor





FIG 18—Chondrodystrophia foetalis (achondroplasic dwarf) age 2?
height 3 feet 10 inches

mal in size The same general type of changes resulting from arrested bone development is seen in the pelvis It is misshapen and flattened as a result of early synostosis and arrested osseous growth[41] The sacrum and coccyx develop normally

The most remarkable and interesting changes are found in the bones of the extremities especially the femur and humerus (Figs 18, 19 and 20) In general these long bones show first of all a shortening of from one third to one half in length in which the epiphysis does not participate[10] The fibula, however, as first mentioned by Marie [r] is relatively longer than the tibia The diameter of the diaphysis is not far from the normal, thus giving to the bones a very short but massive appearance The shaft may be straight but is more often curved to a pronounced degree As the bones are hard and compact, fractures are but very rarely seen

The malformation of the epiphysis is quite as striking as that of the diaphysis This portion of the bone shows an enormous hypertrophy which takes the form of an irregular mushroom growth In consequence of this cartilaginous overgrowth motion in the joints of the extremities often is limited and sometimes entirely lost More or less flexion is the rule The joint surfaces are normal and arthritis does not occur Notwithstanding the fact that the bones of the hands and feet develop from cartilage the involvement in them is not very conspicuous

On section the affected bones present very abnormal and varied appearances There is evidence that periosteal bone production is active where endochondrial ossification is wanting The cortex of the shaft is thickened and the periosteum active Many osteoblasts are present For the most part a fairly regular system of trabeculae is found The medullary canal often is wanting but the marrow spaces are numerous and enlarged The marrow is vascular and rich in round and spindle cells as well as in red blood corpuscles Giant cells sometimes are abundant suggesting bone absorption Bone absorption does occur and may progress to such an extent that fractures take place but such an occurrence is rare Osteosclerosis occasionally complicates the picture

The huge cartilaginous ends of the bones show even greater changes than are found in the shaft for they are the site of the primary disorder in the disease In some cases the tissue has the structure of normal hyaline cartilage in a state of active growth More commonly the cartilage structure is grossly abnormal and shows evidence of having undergone mucoid degeneration MacCallum describes ' a peculiar disappearance of the normal homogeneous matrix so that the cartilage cells are single or in little groups which hang together in a network Connective tissue metaplasia is common Vacuolation has been mentioned frequently The most important and characteristic change in the cartilage in chondrodystrophia foetalis is the marked aplasia in the zone of ossification Kauf

mann [1] says in all cases there is a more or less complete inhibition of the normal row formation of the proliferating cartilage cells in the preparatory stage of ossification It is this aplasia in the zone of proliferating cartilage at the epiphyseal line which explains the diminution in the power of linear growth in the long bones[14] A peculiar and constant lesion in all severe cases is the continuation of the periosteum inward for a variable distance between the diaphysis and epiphysis as was first noted by Urtel[4]

Symptoms

The symptoms are essentially objective and have been mentioned already under pathology The moderately large head of the brachycephalic type rather small and cretinoid features depression of the root of the nose prognathism normally developed trunk contrasting with the short and plump extremities lordosis trident hands protuberant abdomen general increase in the subcutaneous fat and loose integument are constant features of the achondroplastic fetus With very rare exceptions these infants are stillborn or die in the early months of life The few who survive the first year or two develop without impairment of their general health and apparently have the same expectation of life as do normal individuals The great majority of adult dwarfs are of this so called achondroplastic type

In early years the adiposity disappears and the skin gradually takes on a normal appearance The fetal deformities of the skeleton persist but otherwise the development of the child is essentially normal Except for occasional instances of hyperplasia of the teeth dentition is not defective Organic functions are normal Kassowitz mentions a relaxed condition of some of the joints especially the knees but such an occurrence is exceptional

The adult achondroplast is a deformed dwarf and with slight modifications due to growth presents the same general characteristics as are seen in the fetal stage (Fig 18) The same decentralization of the body is present the central point being at the xyphoid cartilage or slightly higher instead of at the symphysis pubis as is the case in normal adults

A very striking feature is the abnormal development of the skeletal muscles which gives the achondroplastic dwarf a strength relatively much greater than the normal man (Fig 18) The posture is erect and the spine perfectly straight except in the lumbar region where there is marked lordosis due to the forward tilting of the sacrum The height of 117 achondroplastic adults was found by Gunther [3] to vary from 89 to 144 cm with an average of 118 cm In only 11 of the entire group did the height exceed 130 cm The ratio of the circumference of the head to the total body length is much greater than in individuals of normal



Fig 19.—Chondrodystrophia foetalis (achondroplasia) X ray of arm of patient shown in Figure 18

Facing 502 (3)

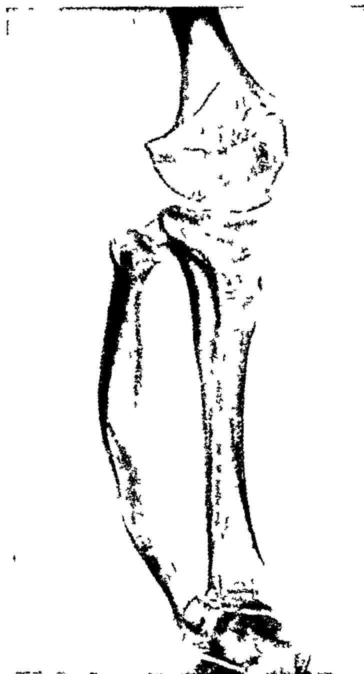


FIG o.—Chondrodystrophia foetalis (achondroplasia) X-ray of lower leg of patient shown in Figure 18

stature A decided brachycephalic or globular type of head, increased cephalic index and prominence of the frontal and parietal portions are constantly present The face actually is large but appears small in consequence of the enlarged calvarium All of the features are somewhat coarse, but the nose in particular shows constant changes The whole nasal region is flattened with an especially well developed retraction at its root The end is hypertrophied and rounded

The extremities are symmetrically and about equally involved, but in both the arms and legs the greatest shortening is in the proximal or root segment, rhizomelia Relative shortening of the tubular bones increases with growth, and the disproportionate size of the epiphyses becomes more marked The arms are so much shortened that the finger tips which normally reach to the mid thigh barely touch the crest of the ilium Complete extension of the elbow joint is impossible and motion in the shoulder articulation usually is somewhat limited The bones are only slightly curved The hands are diminutive, short broad and pudgy All of the fingers are of about equal length and tapering and distal to the second joint are separated from each other like the spokes of a wheel or trident, hence the name main en trident ' (Marie)

Equally marked dwarf characteristics are present in the legs, and the femur and tibia are apt to show considerable bowing (Figs 19 and 20) Malposition of the knee joint and relaxation of the joints of the toes are common

The sexual organs are normally developed, while an exaggeration of sexual functions is not unusual This enhanced sexual appetite is common to both sexes and is probably a compensatory reaction to physical inferiority A considerable list of abnormalities may be cited as occasionally seen in achondroplasia harelip, micrognathy and agnathy myxedema hydrocephalus, but these are non characteristic symptoms of the disease Mental development is normal, but many achondroplastic dwarfs as a result of the inferiority which their deformity incurs, tend to show personality defects The endocrine organs are normal [4]

X rays (Figs 19 and 20) show particularly characteristic appearances in achondroplasia which are unlike those seen in rickets and cretinism, the two conditions with which the disease sometimes is confused They confirm the pathological findings as regards the size and shape of the affected bones Fussell and Pancoast[1] have described the abnormalities in growth of the epiphysis and shaft as well as in osseous structure They consider the appearances in the hands and feet especially as peculiar and unique The abrupt expansion of the shaft at its epiphyseal end and the deficient and irregular ossification at this point are important features A localized and very abrupt bowing at the upper end of the tibia and lower end of the femur also contrasts with the broad curve of rickets The shaft of the long bones is dense and fairly uniform All ridges for the attachment of muscles are enlarged and the normal angles accentuated[18]

Course and Prognosis

Nearly all cases die between the seventh and ninth month of intrauterine life Of those living at birth the majority succumb within the first few months The few who survive the first year probably representing the mild type of the disease seem to have a normal chance of life In spite of the dwarfism these individuals often possess a physical vigor comparable to the normal Numerous cases are found in the literature who have lived to extreme old age Since achondroplasia is primarily the result of deficient bone growth the disease does not advance after the time when bone growth normally ceases

Diagnosis

The principal diagnostic features of achondroplasia are the fetal origin macro cephalic and brachycephalic head depressed root of nose and prognathism normal trunk stunted growth of the extremities with resulting decentralization of the mid point of the body bone deformities lordosis main en trident general excess of subcutaneous fat with thickened loose skin protuberant abdomen normal mentality and the x ray findings If these characteristics are kept in mind achondroplasia should never be confused with any other condition

Differentiation from fragilitas ossium is discussed under that disease Mongolism bears no real resemblance to achondroplasia The subject of the former *is an idiot shows facial characteristics entirely unlike those of achondroplasia and* suffers from none of the skeletal changes of the latter Cretinism is confused sometimes with this disease since the chondrodystrophic infant often presents certain changes in the face which are suggestive of this disorder The cretin is feeble minded and shows the objective signs of myxedema Rickets probably is a rare complication of achondroplasia in children but bears no close resemblance to it The x ray findings will differentiate the process in the two conditions

Treatment

Beyond the employment of measures to improve the general nutrition treatment is of no avail *Prosthetic measures may aid in overcoming deformities*[5] For a further discussion of chondrodystrophy as a cause of dwarfism the reader is referred to Vol III Chapt XIX of Oxford Medicine

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Course and Prognosis

Nearly all cases die between the seventh and ninth month of intrauterine life. Of those living at birth the majority succumb within the first few months. The few who survive the first year probably representing the mild type of the disease seem to have a normal chance of life. In spite of the dwarfism these individuals often possess a physical vigor comparable to the normal. Numerous cases are found in the literature who have lived to extreme old age. Since achondroplasia is primarily the result of deficient bone growth the disease does not advance afte the time when bone growth normally ceases.

Diagnosis

The principal diagnostic features of achondroplasia are the fetal origin, macrocephalic and brachycephalic head, depressed root of nose and prognathism, normal trunk, stunted growth of the extremities with resulting decentralization of the mid point of the body, bone deformities, lordosis, main en trident, general excess of subcutaneous fat with thickened loose skin, protuberant abdomen, normal mentality and the x ray findings. If these characteristics are kept in mind achondroplasia should never be confused with any other condition.

Differentiation from fragilitas ossium is discussed under that disease. Mongolism bears no real resemblance to achondroplasia. The subject of the former *is an idiot, shows facial characteristics entirely unlike those of achondroplasia and* suffers from none of the skeletal changes of the latter. Cretinism is confused sometimes with this disease since the chondrodystrophic infant often presents certain changes in the face which are suggestive of this disorder. The cretin is feeble minded and shows the objective signs of myxedema. Rickets probably is a rare complication of achondroplasia in children but bears no close resemblance to it. The x ray findings will differentiate the process in the two conditions.

Treatment

Beyond the employment of measures to improve the general nutrition, treatment is of no avail. *Prosthetic measures may aid in overcoming deformities.* For a further discussion of chondrodystrophy as a cause of dwarfism the reader is referred to Vol. III, Chapt. XIX of Oxford Medicine.

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Incidence — This is a relatively rare condition Neller [7] found only 24 cases recorded in the literature prior to 1941 Lichtenstein and Jaffe on the other hand have encountered personally 23 cases of the disorder in which the diagnosis was established on an anatomical basis In addition these authors found 32 cases described in the literature up to 1937 Between 1937 and 1942 43 cases were reported which with the 15 cases added by Lichtenstein and Jaffe and those in several more recent papers[7, 11, 30] make a grand total of about a hundred cases reported to date

It is probable that the condition is much commoner than the literature indicates only the more complete forms of the disease in which marked deformity or endocrine disturbances are manifested having been reported The great majority of instances in which a single bone is involved usually have escaped notice or been considered as atypical forms of a simple benign bone cyst Fibrous dysplasia of bone represents probably the second most common systemic anomaly of osseous development only dyschondroplasia exceeding it in frequency of occurrence

Etiology

The etiology of the disease is obscure The condition probably represents some congenital disorder of the germ plasm which manifests itself in dysplasia of the bones abnormalities in pigmentation of the skin functional disturbances in the endocrine system and rarely in other dysplasias of mesenchymal tissues

There is no reason to suspect any abnormality of parathyroid function as responsible for the observed lesions in the bones The sexual precocity which sometimes is observed has been attributed to abnormality in hypothalamic function due perhaps to pressure by the endostoses occurring in the base of the skull The hypothesis that both the sexual precocity as well as the bone lesions are due to an overproduction of estrogen is based on the view that the changes in the bones are analogous to the development of the air sacs in the bones of the bird However this interesting hypothesis is untenable An overproduction of estrogen such as occurs for example in granulosa cell tumors of the ovary induces no fibrous dysplasia of the bones nor can the estrogens induce ovulation such as occurs in the precocity which is manifested in fibrous dysplasia of bone There is also no basis for the view that the condition represents a dyspituitarism

The predominantly unilateral distribution of the lesions would exclude any hormonal metabolic or systemic disorder as responsible for the condition Nor does it appear likely that it results from a neurotrophic disorder as has been suggested Histologically the lesions in the bones show no evidence of either inflammatory or neoplastic tendencies and hence these may be excluded also as causative agents

Part VIII

FIBROUS DYSPLASIA OF BONE

Introduction

This is a condition the nature of which only recently has been clarified and given the status of a clinical entity In the earlier literature instances of the disorder were designated by a variety of titles representing variants of the theme of osteitis fibrosa [1] or osteodystrophia fibrosa[11,1,13,0,5] with prefixes such as unilateral disseminated or polyostotic' It has been looked upon as a regional or unilateral form of von Recklinghausen s disease of bone[4] or as a juvenile form of Paget s disease of bone Albright [3] and his associates in 1937 stressed the extra osseous manifestations which frequently occur in the disorder and some recent writers [1,14] have therefore referred to the disease as Albright s syndrome The studies of Lichtenstein and Jaffe[18,19] have clarified the problem and demonstrated the specific nature of the disorder and the various forms in which it may occur

Synonyms — Fibrous dysplasia of bone polyostotic fibrous dysplasia Albright s syndrome osteodystrophia fibrosa unilateral disseminated or generalized osteitis fibrosa regional or unilateral von Recklinghausen s disease of bone, juvenile Paget s disease regional fibrocystic disease osteodystrophia fibrosa non generalized fibrous osteodystrophy osteite fibro geodique disseminée fibro cystic bone disease as well as by many other terms

The term fibrous dysplasia suggested by Lichtenstein and Jaffe[19] seems most appropriate for it describes the pathological condition in the bones which is the basic disturbance in the syndrome Although having the appearance of a disseminated osteitis fibrosa this term is undesirable since the condition is not an osteitis and the expression osteitis fibrosa leads to confusion with other conditions so designated Since precocity and pigmentation are present only in the most severe cases the use of an eponym applicable only to these also is misleading

Definition — A condition affecting one several or many bones the graver cases of which may present abnormal pigmentation of the skin, premature sexual development hyperthyroidism or still other extraskeletal abnormalities' (Lichtenstein and Jaffe[19])

involved in the fibrous dysplasia are found to be normal which is not the case in hyperparathyroidism The lesions consist of a replacement of the normal bone by fibrous tissue of variable density Unlike bone cysts which they resemble roentgenologically the lesions are solid with a gritty and spongy consistency due to the presence of microscopically visible spicules of poorly formed bone Islands of hyaline cartilage are found also on microscopical examination which also differentiates the condition from the fibrous osteitis observed in hyperparathyroidism renal rickets some stages of Paget s disease and infectious processes

The histological appearance of the lesion is considered by most observers to be indistinguishable from that seen in other conditions in which osteitis fibrosa occurs However when sufficient material is at hand for study the microscopical picture according to Lichtenstein and Jaffe[19] is specific and pathognomonic of the disorder and differentiable from other superficially similar involvements of bone There is some question whether the so called ossifying fibroma or fibrous osteoma [* *] of the jaw represents a monostotic form of fibrous dysplasia

In addition to the occasional islets of cartilage and spicules of bone mentioned above the lesions consist mainly of spindle cells with an oval pale staining nucleus and an indistinct cytoplasmic outline The detailed histological appearance may vary from area to area The connective tissue may be composed of immature cells loosely arranged in whorls or may appear to be poorly cellular and collagenous or myxomatous with cystic softening Only rarely are cystic spaces containing fluid present Nests of giant cells may be found but these usually are smaller than those encountered in giant cell tumors A few nests of foam cells may be observed also and have led to a mistaken diagnosis of xanthomatosis

The observed pigmentation in the skin consists of deposits of melanin in the corium and accumulations of melanoblasts in patchy paravertebral areas on the *buttocks sacral and lumbar regions the chest and the back of the neck These* pigmented areas tend to occur on the same side as the osseus lesions and show no neurological distribution

SYMPTOMATOLOGY

Except for areas of pigmentation evident at birth and the intestinal disturbances and severe jaundice present in the neonatal period the symptoms of the disease are insidious in development and referable to the bony lesions sexual precocity and other abnormalities noted in the more severe forms of the disorder Deformity a limp and pain in the lower extremity usually appear in late childhood or adolescence Pathological fracture may draw attention to the lesion in the bones Bowing of a limb deformity of the hip coxa vara affecting one side

The fact that the condition is not hereditary would indicate that the alteration or mutation responsible for the disorder occurs in the somatic cells during early embryonic life and not in the germ cells The most reasonable assumption is that the condition results from multiple embryonic defects affecting several systems which would account for the diversity of the observed clinical picture The disorder of the bones probably is the result of an abnormality in a single dominant gene the associated abnormalities are the result of multiple environmental influences on this single gene[1]

Age — The disease being congenital tends to manifest itself during early life The pigmentation which occurs in the more severe cases, will be evident at birth There is a high incidence of icterus gravis neonatorum and gastrointestinal disturbances in infants who later manifest the disorder, and this may call attention to its existence in these cases The sexual precocity, which is limited almost entirely to the female may appear as early as the second year of life

In patients in whom there is a minimal involvement of the bones the disease may only be recognized accidentally in later life

Sex — The disease occurs more frequently in the female than in the male, the ratio of females to males being approximately 10 to 7 in the cases cited in the literature

Pathology

The lesions in the bones are the essential and central feature of the syndrome, being present in all cases while the other manifestations are found only in the severer cases of the disease The condition may be limited to a single bone, monostotic or a part of a bone merostotic, as was the case in 15 of the 87 cases analyzed by Lichtenstein and Jaffe[19] The single bones affected are in the order of frequency the ribs clavicle maxilla tibia femur In 12 of the 87 cases there was involvement of several bones of a single limb, monomelic In 5 there was a limited involvement of 2 or 3 isolated bones In 29 of the cases the skeletal involvement was more extensive but moderate and predominantly unilateral in distribution In the remaining 26 cases many bones were affected polyostotic In the group of 51 cases collected by Falconer, Cope and Robb Smith[10] the femur was affected in every case the tibia and fibula in 48 of the cases and the other bones in the following order of frequency pelvis humerus radius and ulna skull, face thorax vertebral column shoulder girdle metacarpals and metatarsals These cases were instances of the more severe polyostotic form of the disease The epiphyses of the bones are almost always free of involvement

Except for their unilateral distribution the lesions in the bones are suggestive of osteitis fibrosa cystica due to hyperparathyroidism, with which the condition often has been confused However, the portions of the bones which are not

is no evidence of parathyroid dysfunction in the disorder There are no striking abnormal findings in the chemical composition of the blood nor in the metabolism of calcium or phosphorus A moderate increase in the blood phosphatase and calcium may occur reflecting perhaps an augmented osteoblastic activity during the active stage of the disorder However the inorganic phosphate content of the blood is not depressed nor is the calcium excretion in the urine increased as in hyperparathyroidism

The blood shows none of the changes observed in certain of the xanthomatoses nor does the urine show the presence of abnormal amounts of the 17 ketosteroids observed in the adrenogenital syndrome

X Ray Findings

The appearance of the osseous lesions in the x ray varies greatly from case to case and usually is not distinctive [7, 8] In most of the monostotic cases one observes an oval area of rarefaction with a well defined but thinned cortex not differentiable from the solitary benign unicameral bone cyst At other times the appearance may simulate that seen in an enchondroma or in a giant cell tumor At times the lesions have a distinctive loculated appearance due to the presence of bony trabeculae or they may have a diffusely mottled or ground glass appearance [9]

Except at points of fracture the outer surface of the thinned cortex shows no periosteal growth of new bone nor the resorption or erosion of the outer surface of the cortex seen in hyperparathyroidism Although the general appearance of the lesions in severe cases is not unlike that seen in the latter disease their unilateral distribution and the fact that neighboring uninvolved areas of the bone are normal and show no rarefaction serve to differentiate the condition roentgenologically The fact that the epiphyses are rarely involved allows one to exclude dyschondroplasia

The skull when involved does not show the rarefaction and pseudocystic appearance often seen in the long bones The facial bones and base of the skull may appear in the x ray to be involved in a sclerotic overgrowth It is this appearance which led to some of the earlier described cases being designated as juvenile forms of Paget s disease This hyperostosis is particularly striking in the base of the skull There may be a disappearance of the diploe and of the sphenoid maxillary and mastoid sinuses and deformity of the sella turcica[10]

Differential Diagnosis

In the more severe cases with the association of numerous bony lesions and pigmentation of the skin the diagnosis usually presents no difficulty The pres

only are characteristic The lesions tend to be slowly progressive during early life assuming a static condition in the adult

When the process involves the bones of the face, there may be marked asymmetry and deformity of the inferior maxilla[7 7] Involvement of the base of the skull may lead to proptosis compression of the optic nerves and failure of vision[13]

Pigmentation is the commonest of the non skeletal manifestations, being present in about one third of the cases Its distribution and nature have been discussed under Pathology The pigmentation may be entirely absent, cover an area less than one square centimeter in size or consist of large patches over the back or thorax True precocity occurs in about one fifth of the patients but is limited almost entirely to the female Falconer, Cope and Robb Smith[10] report an instance of precocious development in a boy nine years old There is actual sexual maturation of the ovaries with menstruation, ovulation and development of the secondary sex characters The notorious case of a girl who gave birth to a child at the age of five is quoted by Albright, in a discussion of the paper by Kornblum[1] as being an example of the disorder The sexual precocity thus is similar to that observed in hypothalamic disturbances and unlike that seen in the adrenogenital syndrome or in granulosa cell tumors of the ovary The fact that the concentration of 17 ketosteroids in the urine is not increased in fibrous dysplasia[10] also reflects the fundamental dissimilarity between the precocity observed in the two conditions

Menstruation may begin as early as the second year of life but usually is not seen until the ages of five to eight The menstrual flow is very irregular and prolonged with intervening periods of amenorrhea

Other evidences of endocrine dysfunction include hyperthyroidism which has been present exclusively in females with one exception Acromegalic features have been described also Gynecomastia and other evidences of feminization have been described in one patient [1]

Growth often may be accelerated during childhood so that the bone age and height of the patients are advanced over their chronological age However with early sexual maturity and premature closure of the epiphyses the ultimate stature may be subnormal

As in the case of certain other congenital disorders of bone the blood vessels may show abnormalities also as in the patient of Stauffer, Arbuckle and Aegerter [7], who had multiple congenital arteriovenous aneurysms

METABOLISM

Although the changes in the bones resemble and frequently have been mistaken for those seen in osteitis fibrosa cystica due to hyperparathyroidism, there

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ence of normal areas of bones contiguous to the lesions their unilateral distribution and the blood chemistry findings should obviate confusion with von Recklinghausen s disease of bone due to hyperparathyroidism The presence of atypical areas suggestive of a reparative reaction may suggest a malignant process, but the benign nature of the lesions usually is evident roentgenologically

The presence of the bony lesions will differentiate sexual precocity due to hypothalamic adrenogenital or gonadal disturbances Xanthomatosis, Schuller Christian s disease and the other lipoidoses may be differentiated by the elevated cholesterol level of the blood in most cases of xanthomatosis, the polyuria and bilateral exophthalmos noted in Schuller Christian disease, the subsidiary findings, splenomegaly hepatomegaly anemia and the differences in the appearance and distribution of the lesions in the bones in many of the lipoidoses

Isolated lesions in the bones require a biopsy and microscopical examination to establish the diagnosis

Prognosis

The prognosis in all but the most severe forms of the disease is good No instance has been reported in which malignant transformation of the lesions in the bones has occurred There is little tendency for the lesions to progress after the period of active growth when they usually become arrested Except for the instances where there is marked deformity hyperthyroidism or arteriovenous aneurysms a normal life expectancy may be anticipated

Treatment

The treatment in any given patient obviously must be determined by the presenting complaints A solitary lesion discovered incidentally usually will require no attention other than a biopsy to establish the diagnosis Solitary bone lesions may be eradicated by thorough curettage and filling the cavity with autogenous bone chips Recurrences however are not uncommon When the lesion involves a rib resection is preferable Radiation is ineffective[19] Where the lesion is large and involves the weight bearing bones or those subject to fracture, a massive autogenous bone graft should be inserted to prevent subsequent fracture and deformity Orthopedic aids, including braces and corrective shoes, may be required also

The precocious puberty requires no treatment although precautions should be taken to avoid pregnancy which may occur even in childhood There is some question as to the advisability of thyroidectomy, where hyperthyroidism is a symptom this operation having resulted fatally in one patient on whom it was performed

PART IX

HYPEROSTOSIS FRONTALIS INTERNA
(*Metabolic Craniopathy*)

INTRODUCTION

The condition designated as hyperostosis frontalis interna or metabolic craniopathy is not strictly speaking a disease of the bones It is a disorder characterized primarily by various metabolic endocrine and neuropsychiatric manifestations It is questionable whether the changes observed in the skull are an essential part of the syndrome or contribute to the clinical picture Nevertheless since these changes in the skull are the only objective finding upon which the diagnosis is based the disease is considered here among primary bone diseases

Synonyms —Metabolic craniopathy[2 26] hyperostosis frontalis interna[20] cranial enostoses[3 4] calvarial hyperostosis[7] cranial hyperostosis of the insane[8] Morgagni s syndrome[7 41] Stewart Morel syndrome[4 41] intracranial osteophytes[18]

Definition —A syndrome characterized clinically by variable and protean manifestations of a metabolic endocrine and neuropsychiatric nature and roentgenologically by a characteristic thickening of the internal tables of the skull

Historical —Hyperostosis of the skull was described first by Morgagni and Santorini[1] in 1765 and has been recognized in the skulls of museum specimens dating from even earlier times Moreau described a case in a priest executed for murder in 1786 The condition was encountered frequently by pathologists during the nineteenth century but was not differentiated from membranous dural calcification puerperal osteophytes Paget s disease of bone acromegaly infectious osteitis circumscribed exostoses and other conditions in which the bones of the skull may be thickened As these conditions were differentiated hyperostosis frontalis interna gradually assumed the status of a pathological entity and roentgenologists began to recognize and describe the condition

As early as 1897 Beadles[8] in a study of the cranial bones of the insane called attention to the extraordinary degree of hyperostosis which ' occurs in the frontal region and with far greater frequency in females He noted that the patients in whom this hyperostosis occurred were cases of chronic mania or

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Part IX

HYPEROSTOSIS FRONTALIS INTERNA
(*Metabolic Craniopathy*)

Introduction

The condition designated as hyperostosis frontalis interna or metabolic crani opathy is not strictly speaking a disease of the bones It is a disorder charac terized primarily by various metabolic endocrine and neuropsychiatric mani festations It is questionable whether the changes observed in the skull are an essential part of the syndrome or contribute to the clinical picture Neverthe less since these changes in the skull are the only objective finding upon which the diagnosis is based the disease is considered here among primary bone diseases

Synonyms —Metabolic craniopathy [28] hyperostosis frontalis interna [9] cranial enostoses [5] calvarial hyperostosis [7] cranial hyperostosis of the in sane[15] Morgagni s syndrome[17,41] Stewart Morel syndrome[14] [41] intracranial osteophytes[16]

Definition —A syndrome characterized clinically by variable and protean manifestations of a metabolic endocrine and neuropsychiatric nature and roent genologically by a characteristic thickening of the internal tables of the skull

Historical —Hyperostosis of the skull was described first by Morgagni and Santorini[11] in 1765 and has been recognized in the skulls of museum specimens dating from even earlier times Moreau described a case in a priest executed for murder in 1786 The condition was encountered frequently by pathologists during the nineteenth century but was not differentiated from membranous dural calcification puerperal osteophytes Paget s disease of bone acromegaly infec tious osteitis circumscribed exostoses and other conditions in which the bones of the skull may be thickened As these conditions were differentiated hyperostosis frontalis interna gradually assumed the status of a pathological entity, and roent genologists began to recognize and describe the condition

As early as 1897 Beadles[3] in a study of the cranial bones of the insane called attention to the extraordinary degree of hyperostosis which occurs in the frontal region and ' with far greater frequency in females He noted that the patients, in whom this hyperostosis occurred, were cases of chronic mania or

such as have passed into dementia." Naito[33] in 1924 published photographs of 9 skulls and Casati[7] in 1926 added 5 cases showing typical x rays of hyperostosis frontalis interna. Grieg[16] in 1928 found 32 instances of "intracranial osteophytes" among 188 crania which he examined in the museum at Edinburgh, among which were a number of instances of hyperostosis frontalis interna.

It was not until 1928 that the condition was recognized as a possible clinical entity. In that year Stewart[45] described 5 patients with unusual clinical features who at autopsy revealed hyperostosis of the skull. He drew attention to the association of mental symptoms and obesity with the localized cranial hyperostoses. Morel in 1929 described the first living case in a patient confined to the Asylum of Bel Air, Switzerland. The symptoms in this case were catalepsy, adiposity, delusions and hallucinations. Van Bogaert[4] in the same year and Schiff and Trelles[4] in 1931 reported other cases and helped to establish the condition as a definite entity. Moore's survey[6, 7] of 6,650 x rays of the skull clarified the field and established criteria for its x ray diagnosis.

During the past decade numerous papers have appeared reporting over one hundred clinical cases[1, 8, 10, 13, 14, 1, 40, 41, 43]. The great frequency with which the condition is encountered by those looking for it has prompted many to assume a critical attitude regarding such observers as overenthusiastic and even questioning the very existence of it as a clinical entity[18, 0]. This skepticism has been engendered in part by the absence of strict criteria whereby one may delimit hyperostosis frontalis interna. Careful differentiation of the condition as defined, e.g., in the classical papers of Moore from other conditions, in which there is thickening of the skull, reveals so close a concordance between symptomatology and roentgen findings as to convince one that it is a clinical entity.

Etiology

Little is known of the pathogenesis of the disorder. It is probably a congenital hereditary condition in which the fundamental disorder lies in the hypothalamus or other vegetative centers of the brain. This assumption would account for the protein metabolic and neurological manifestations of the disorder. According to this view the changes in the skull are only one manifestation of the syndrome and need not be present in every case.

A variety of theories have been advanced to explain the pathogenesis of the disorder. Morel found a lesion characterized by excess pigment and fat in the cells of the wall of the third ventricle in one case but subsequently[30] retracted the view that this was responsible for the disorder. The view that the pituitary gland is related in some way to the pathogenesis of the disorder has been championed by several observers[1, 13]. Bridging of the sella turcica is observed frequently

in the x rays of patients suffering from the disorder and the endocrine and metabolic manifestations are those commonly associated with hypophyseal disease Stewart[8] observed fibrous displacement of the hypophysis in one of his cases However the view that the condition results from dyspituitarism is not compatible with modern knowledge of the function of this gland

Morel suggested that the close attachment of the dura to the frontal bone produces tension which in turn stimulates the production of hyperostosis This view fails to account for the localized sessile or flat type of hyperostosis[7] nor for the metabolic and neurological symptoms which may be present before the changes in the skull are prominent Schiff and Trelles[15] believed that the condition was a result of trauma but although a history of a blow to the head is elicited frequently it is unlikely that this is the origin of the disorder

Several authors[16, 9] have expressed the view that the parathyroid glands or some abnormality in mineral metabolism is responsible for the observed changes in the skull However only rarely are any appreciable changes in the calcium or phosphorus levels of the blood observed and hence these views are untenable

In a number of the recorded cases which have come to autopsy atrophy of the cortical area of the frontal lobes has been observed[4] Earlier workers believed this atrophy to be the cause of the observed thickening of the skull which they looked upon as a reaction to compensate for the loss of intracranial contents Such a view however is contradicted by the fact that marked degrees of hyperostosis may occur in young individuals before cortical atrophy has taken place and by the observation that pronounced thickening may occur on the side opposite to that in which the atrophy occurs[4]

Age —Although the condition seldom is demonstrable by the roentgenogram before middle age the history of the patient usually reveals a slow and insidious development of the disorder which probably begins in early life[1] The earliest case on record in which the hyperostosis was evident in the x ray was aged 10[7] and several cases are on record in which the disease was recognized and the changes in the skull already pronounced before the age of 20 In most cases however the patient first comes to the attention of the physician after the age of 30 and the majority of the patients are seen first during the fourth and fifth decades of life

Sex —The disease is predominantly one of the female sex In Moore s study 97 per cent of the patients were women All of the 17 cases reported by Carr[6] were women as were also the 20 patients observed by the present author The disease thus is relatively uncommon in the male

Incidence —It is difficult to state the exact frequency with which the disorder occurs as this depends upon the criteria upon which the diagnosis is based Thus Henschen[18] found what he called hyperostosis verrucosa frontalis in

terna in 50 per cent of all females over 50 years of age, many of whom were free of any symptoms Likewise Tager Shelton and Matzen[50] in an examination of skulls in 492 consecutive patients found what they considered instances of hyperostosis calvarii interna' in 13 4 per cent These authors as well as Henschen[50], concluded therefore, that hyperostosis was of no clinical significance and a part of no specific syndrome

In contradiction to the results just cited are those obtained by most other investigators Thus Moore found an incidence of only 1 2 per cent This is approximately the incidence with which the condition is observed in a general hospital population On the other hand the disease, as is to be expected is much more prevalent in institutions for the insane Thus, Eldridge and Holm[11] observed an incidence of 25 per cent among 200 patients admitted to St Elizabeth s Hospital Washington

The condition certainly is not as rare as one would be led to believe by the lack of attention given to it in medical textbooks and those keeping it in mind will encounter many cases conforming to the classical picture manifested by the disorder

Heredity — There is a definite familial tendency, and it is not uncommon to find several affected members of a single family The condition seems to be an expression of a dominant gene[17 1 44]

Pathology

Since longevity is not affected by the disorder few of the patients have come to autopsy, and little is known of the pathology of the disease except for the changes in the skull If the view expressed under etiology be correct, one would anticipate cytological evidence of abnormality in the hypothalamus or other centers in the brain Such studies are urgently needed to elucidate the nature of the disorder

The skull is the only site of any abnormality in the osseus system with gross thickening of a centimeter or more of the internal tables [5] (Figs 21A and 21B) The newly formed bone consists of cancellous bone covered by a thin layer of compact bone to which the dura is adherent The frontal bone usually is affected but the hyperostosis may involve also the parietal or occipital bones or be diffuse The thickening usually is symmetrically distributed lying on either side of the sulcus of the superior longitudinal sinus but asymmetry is noted occasionally, particularly as regards the deposition of nodular excrescences[16 4] The outer table of the bone is never involved which is important in differentiating the condition from other hyperostoses of the skull The new bone does not form beyond the coronal suture and may be either nodular or sessile in form In rare cases the orbital



Fig 1A — X ray of skull in hyperostosis frontalis interna showing the marked thickening of the internal tables of the skull (Courtesy of Dr J I Rousseau)

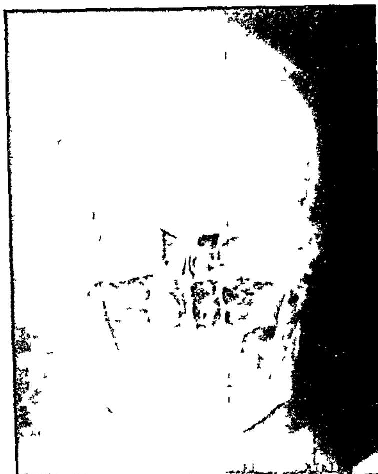


Fig 1B —Hyperostosis frontalis interna X ray of skull in anteroposterior view in a patient in whom proliferation had produced irregular or island like masses of thickened bone on either side of the midline of the frontal bone (Courtesy of Dr Felix G Fleischner Roentgenologist to Beth Israel Hospital Boston)

plate of the frontal bone may be involved chiefly Calcification of the falx cerebri also is not uncommon

In a few cases degenerative changes have been noted in the hypothalamus, cerebral cortex and pituitary[11] However few patients have come to autopsy, and in some no obvious changes have been found to account for the disorder[39]

Symptomatology

The symptoms are protean and variable In general, however, they consist of certain psychic and neurological changes endocrine disorders and metabolic

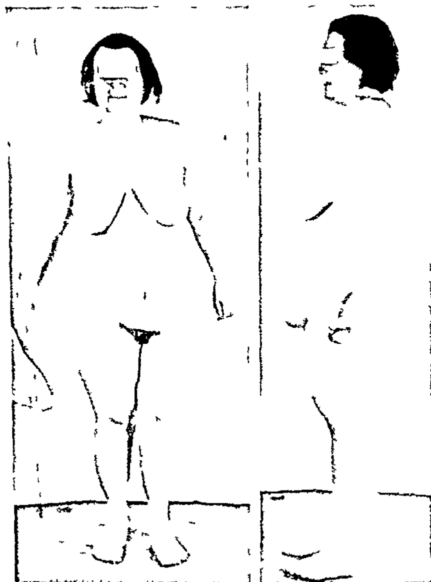


FIG 22—Patient with hyperostosis frontalis interna A 27 year old woman showing the rhizomelic obesity and megalomastia common in hyperostosis frontalis interna The patient also manifested neuropsychiatric changes hysterical paralysis personality changes characteristic of the disorder

disturbances One or another of these may be predominant, but in the classical cases all are present to some degree

The psychiatric changes conform to no specific syndrome In Eldridge and Holm's[11] patients 13 of the 2– types of psychoses recognized by the American Psychiatric Association were noted Hyperostosis frontalis interna is twenty times as frequent in hospitals for the mentally deranged as in normal individuals, and one frequently encounters a history of insanity in relatives of patients manifesting the disease

In many patients the psychiatric manifestations are not of a degree to incapacitate the individual but are nevertheless sufficiently striking to suggest that the patient is suffering from this disorder, particularly when associated with disturbances of a metabolic and endocrine nature Schiff and Trelles[45] describe the psychiatric disturbances as consisting of (1) intellectual slowness with depression and anxiety ( ) disturbances of temperament and character and (3) protective neuroses There is usually a history of long standing personality changes egocentricity hypochondriasis psychoneurosis nervousness, a tendency to worry and depression being present frequently In a few cases homicidal and criminal tendencies have been present

The neurological symptoms also are diverse and follow no definite pattern Headache continuous with paroxysmal exacerbations, is present in about 80 per cent of the patients It is commonly frontal but may be occipital or be referred to the top of the head The headache often is disabling Easy fatiguability and muscle weakness are frequent complaints Dimness of vision, diplopia, dizziness and disturbances of gait and equilibrium are not uncommon Epileptiform seizures of the Jacksonian type narcolepsy motor difficulty in speech, neuralgia and palsies involving the cranial nerves sensory disturbances with numbness and tingling transitory hemiplegia and hemiparesis are observed also in about 10 per cent of the patients[3 38 38] A general hypersensitivity of the surface of the body and other signs of meningeal irritation are observed sometimes[17] Insomnia is a frequent complaint

The principal metabolic disturbance is manifested by obesity (Fig 22) similar to that observed in so called pituitary ' disorders It is of the rhizomelic type with megalomastia Glycosuria and hyperglycemia also are observed frequently and like other forms of diabetes not of pancreatic origin are relatively refractory to insulin therapy Carr described an abnormal excretion of creatine in the urine[6] The blood levels of calcium and phosphorus deviate only rarely from normal limits Rossier and Secretan[4] stress the absence of the normal specific dynamic action which follows the ingestion of protein

Amenorrhea and other evidences of ovarian failure are common, but in many cases normal menstruation and reproductive function are present Hirsutism i

also a frequent finding (Fig 3) but usually this is unaccompanied by other evidences of virilism, a male voice or enlargement of the clitoris In some patients however these may be present

Hypertension occurs in many of the patients manifesting hyperostosis frontalis interna This has been considered as a coincidental occurrence of hypertensive cardiovascular disease rather than as an essential part of the syndrome[1] However the frequency with which hypertension is observed would lead one to suspect that it is another of the protean manifestations of the disorder



Fig 3—Head of a patient with hyperostosis frontalis interna Note the marked hirsutism and spacing of the teeth in a patient with hyperostosis frontalis interna who also manifested amenorrhea obesity reduced glucose tolerance with glycosuria but only insignificant neuropsychiatric changes

X Ray Findings

The roentgenogram of the skull (Figs 21A and 21B) is the only objective method for establishing the diagnosis[1, 2] The symptoms may appear however before the changes in the skull are evident and in rare instances the x ray findings are found in apparently normal individuals not suspected of having the disease Whether such patients ultimately develop characteristic symptoms is not known

The changes in the skull are classified by Moore according to their regional

distribution into four types, (1) hyperostosis frontalis interna, (2) nebula frontalis (3) hyperostosis calvariae diffusa and (4) hyperostosis frontoparietalis These different types are bilateral and symmetrical in distribution and all may be present in one individual In hyperostosis frontalis interna the newly formed bone is deposited on the inner table of the squama frontalis It may extend to the orbital plates of the frontal bone and at times is limited to these structures In the type designated as nebula frontalis ' there is a triangular or ovoid area of newly formed bone in the squama frontalis with its broad base in the sagittal plane and limited to the diploe This variety of hyperostosis may be difficult to demonstrate in the x ray unless brought into profile In " hyperostosis calvariae diffusa there is a general increase in the bone comprising the diploe of the vault of the skull It too may be difficult to detect The hyperostosis frontoparietalis resembles the two types just described except for its location in the frontoparietal region Maximum thickening occurs at the central points of the squamous portion of the frontal and parietal bones producing an even grooving of the skull at the coronal and sagittal sutures

The different types just described occurred in 1 44, 1 14, 0 6 and 0 3 per cent, respectively of 20 000 x rays of the skulls of 6 650 individuals studied by Moore Calcification of the falx cerebri was noted in all four types, the region of attachment of the falx remaining free The irregular thickening of the vertical part of the frontal bone may be smooth or irregular with numerous spikes or nodular indurations The outer table of the skull never is involved Areas of thinning may be observed in the frontal or other cranial bones involved [1]

The various types of hyperostosis described above do not represent specifically distinct varieties for they are frequently associated in the same individual Moreover patients manifesting one of the more infrequently occurring varieties may in time show more diffuse involvement as the disease progresses[4]

Differential Diagnosis

The classical case of hyperostosis frontalis interna usually may be suspected without difficulty by the combination of neurological and psychiatric symptoms and the metabolic and endocrine manifestations of the disorder An x ray of the skull confirms the diagnosis Where obesity and virilism are present the condition is mistaken frequently for Cushing s syndrome, and many of the patients so diagnosed in the past probably have been instances of hyperostosis frontalis interna The long duration of the latter disorder the absence of the typical purplish striae and the osteoporosis characteristic of Cushing s disease and the presence of psychiatric and neurological symptoms usually permit a clinical differentiation of the two conditions The x ray findings in the skull confirm the

diagnosis A determination of the 17 ketosteroid excretion also is useful since unlike Cushing s disease this is normal in hyperostosis frontalis interna

In patients with predominating neurological symptoms differentiation must be made from incipient paresis, multiple sclerosis brain tumor and hysteria The symptoms in many cases suggest a psychoneurosis The thickening of the skull must be differentiated from localized forms of leontiasis o sea and of osteitis de formans to which the changes in the skull in ome cases bear a close resemblance These conditions may be recognized by the other characteristic changes It must be differentiated also from the generalized thickening of the skull observed in the senile and from cranial osteophytes Confusion with the former condition has been responsible for the high incidence of hyperostoses reported by some ob servers leading them to regard the condition as a non specific change rather than a clinical entity

Among other conditions to be differentiated in the x ray are osteosarcoma osteomyelitis of the frontal bone and localized syphilitic osteitis The symmetri cal distribution and limitation of the bony overgrowths to the internal table and diploe of the skull in hyperostosis frontalis interna permits easy differentiation of these conditions

Course and Prognosis

Hyperostosis frontalis interna is a progressive chronic disorder The more se vere cases in which mental symptoms predominate may terminate in dementia The majority of the cases show little progression with long continued morbidity The life expectancy is not reduced appreciably

Treatment

Various therapeutic procedures have been suggested but their efficacy is ques tionable nor can any rational form of therapy be anticipated until the patho genesis of the disorder is elucidated Chondroitin in do es of 2 5 to 3 5 gm daily has been used [1], but its value is questionable Because of the creatinuria seen in the disease Carr[8] suggested the use of aminoacetic acid which may be given in the form of gelatin to overcome the weakness

In patients in whom there is evidence of an increased intracranial pressure, episodes of Jacksonian epilepsy or compression of the optic nerves due to hyper ostosis of the orbital plate surgical intervention is indicated but has not been re ported thus far as accomplished

Irradiation of the pituitary frontal bone and hypothalamic area has been performed with questionable results Thyroid extract posterior pituitary liquid

ergotamine tartrate, fever therapy and parathyroid hormone have been used without effect [1] Rossier and Secretan[4] report an amelioration of symptoms in some cases following the injection of extracts of the anterior pituitary gland

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Part X

OSTEITIS FIBROSA CYSTICA

Introduction

The term osteiti fibrosa or fibrocystic disease of bone refers to any lesion in which osseous tissue is replaced by fibrous tissue with the formation at times of cysts or benign giant cell tumors The condition may be general or local in distribution It is not inflammatory and hence the term osteitis is a misnomer Fibrous osteodystrophy would be a more appropriate designation Osteitis fibrosa is not due to a single etiological agent nor is it a clinical entity but represents a non specific reaction which may result from a variety of causes Some of these are recognized as definite clinical disorders of known etiology and in these the occurrence of osteitis fibrosa is only one manifestation of the disorder However, fibrocystic disease of bone also occurs in a localized form under conditions in which no exact etiological cause may be demonstrated The prognosis and method of treatment in any given case will differ and hence despite certain superficial resemblances of all cases of osteitis fibrosa it is necessary to treat them separately depending on the known or presumed etiology of the different forms in which the condition is observed

Synonyms — The condition was formerly designated as Allgemeine Hyperostose des Skellettes mit Cystenbildung (Virchow) Osteomalacia mit Cystenbildung (Hirschberg[56]) Tumorbildende Osteitis Deformans (Sternberg[8]) Osteitis Fibrosa Osteoplastica (von Recklinghausen[85]) Ostitis Fibroplastica (Franke) Osteodystrophia Juvenalis Cystica (von Mikulicz[4, 73])

More recently the terms osteitis fibrosa cystica generalisata von Recklinghausen s disease of bone parathyroid osteitis hyperparathyroid bone disease have been applied to the condition when secondary to hyperparathyroidi m The terms osteitis fibrosa localisata unicameral bone cyst and giant cell tumor are applied to the single lesions depending upon their histological appearance Fibrous dysplasia of bone[70] regional fibrocystic disease non generalized fibrous osteodystrophy[38] osteitis fibro a disseminata[106] usually are employed to designate the disseminated or multiple lesions of congenital origin which are now recognized as a separate form of the disorder When accompanied by endocrine disorders particularly sexual precocity the condition has been designated as Albright s syndrome

Definition — Osteitis fibrosa may be defined as a condition in which the bone or its marrow cavity is displaced by fibrous tissue Because of the tendency of such lesions to undergo degeneration or hemorrhage, they become cystic and hence the term cystica is often added to their designation The term is used also to include the benign giant cell tumor the matrix of which consists of fibrous tissue and which is now generally accepted as being related to localized osteitis fibrosa

Historical

The disorder is one of the last of the miscellaneous group of bone disorders to be classified properly and to be differentiated from sarcoma with which the benign giant cell tumor in particular was long confused Hirschberg[56] in 1889 gave a very exact description of the pathology of the bones in cases previously designated as multiple cystic sarcoma but he regarded the condition as a late stage of osteomalacia with cyst formation multiple fractures and secondary development of sarcoma Von Recklinghausen[93] in 1891 first separated fibrocystic disease from other bone disorders in which there is degeneration and weakness of the osseous tissue However he considered the disorder as a clinical entity of unknown etiology

It is only during the last two decades that some semblance of order has been introduced in our concept of the relation between the various forms of osteitis fibrosa The role of hyperparathyroidism in inducing certain cases of osteitis fibrosa generalisata has been established firmly and has allowed the separation of this form of the disorder from that in which osteitis fibrosa is secondary to other disorders or constitutes a part of other syndromes

Classification

Although all cases of osteitis fibrosa have many common features insofar as the gross and microscopic appearance of the lesions is concerned it is more convenient to classify and discuss separately the various conditions which give rise to fibrous osteodystrophy Depending upon whether they occur as localized disseminated or generalized lesions throughout the skeleton it is customary to speak of 1) osteitis fibrosa localisata 2) osteitis fibrosa disseminata and 3) osteitis fibrosa generalisata adding the term cystica if the lesions are also cystic. This classification ignores the etiology of the disorder indicating only the extent of the lesions The same etiological agent e g hyperparathyroidism, may induce localized disseminated or generalized lesions as may also the condition designated as fibrous dysplasia of bone Hence the above mentioned classification is fundamentally unsound However osteitis fibrosa localisata has been used to designate isolated lesions including the giant cell tumor and bone cyst, osteitis fibrosa gene

ralisata to indicate the osseous changes associated with hyperparathyroidism and osteitis fibrosa disseminata to designate fibrous dysplasia of bone

Classified as to their etiology we may divide cases of osteitis fibrosa into 1) the solitary lesions due presumably to some localized defect in the bone of unknown etiology and including the unicameral bone cyst and the benign giant cell tumor 2) the generalized disturbance secondary to hyperparathyroidism 3) the local or disseminated lesions occurring as the principal manifestation of fibrous dysplasia of bone or at times seen in association with neurofibromatosis 4) the reaction to decalcification of the bones secondary to renal or other disturbances causing osteoporosis

In the following sections osteitis fibrosa will be discussed under the above four headings

OSTEITIS FIBROSA LOCALISATA

Osteitis fibrosa occurs most frequently as a solitary lesion osteitis fibrosa localisata which may be in the form of the benign giant cell tumor of bone or when the lesion progresses to cystic degeneration gives rise to the solitary unicameral bone cyst As indicated in the following sections a localized solitary lesion may occur also in several conditions which are recognized as clinical entities for example in hyperparathyroidism or fibrous dystrophy of bone The present discussion will therefore be limited to those lesions in which other disorders can be excluded and in which there is reason to believe that the disorder represents a purely local phenomenon unrelated to any systemic disorder [9 47 91]

The localized lesion now under discussion expresses itself in one of three pathologically distinct forms 1) as osteitis fibrosa in which the lesion consists primarily of fibrous tissue 2) as a bone cyst and 3) as the giant cell tumor All of these according to present-day pathological concepts are fundamentally related some even regard them as representing stages of development of the same primary lesion In support of this view is the fact that they exhibit many similarities of clinical appearance and behaviour and occur at times together as in hyperparathyroidism or in intermediate forms[9 14]

However there are certain well-defined differences in their pathological appearance and clinical behaviour

Isolated Lesions of Osteitis Fibrosa

The term osteitis fibrosa localisata or cystica in its more limited sense is used to refer to those isolated lesions in bones which are found in the cavities of the shaft of the bones and which are filled with a firm cellular fibrous tissue These localized lesions of osteitis fibrosa usually are found in children and young adults

before the age of 20 This has been considered as evidence of their origin from a congenital defect in the bone but may be explained also by the fact that the growth and developmental activity of the bones in the young makes them more reactive to any inciting agent such as trauma or hemorrhage, which may be the cause of the disorder[65]

Like the bone cysts to be described next they are found most commonly in the upper shaft of the femur humerus and tibia, occasionally in other sites such as the radius ulna fibula ilium, sacrum, ischium calcaneum, vertebra, metatarsals metacarpals phalanges ribs or pubis

The cause of localized lesions of osteitis fibrosa is not established They have been attributed to trauma, circulatory changes, infection, congenital defects etc Attempts to produce the lesions experimentally by trauma have failed However, the identity of the localized form of osteitis fibrosa to that found in the generalized one, which is secondary to hyperparathyroidism, suggests that they both represent a reaction to a similar local inciting agent, which in the case of the isolated lesion probably is found in the bony tissue, while in the generalized form it is a response to the changes in the bone induced by the decalcification secondary to hyperparathyroidism

In local osteitis fibrosa there is a focal area of osteolysis usually at the end of the metaphysis of one or rarely of several of the long bones There may be cystic degeneration, which in the x ray gives the appearance of a multiloculated lesion, which is central in position and gives a fusiform expansion of the shaft of the bone with thinning of the cortex Spontaneous fracture is common, occurring in about half of the cases of the bone cysts It is less apt to occur in benign giant cell tumor

The localized lesion of osteitis fibrosa consists of a firm yellowish white area in the medullary cavity which on microscopic examination reveals a substitution of the marrow cells by fibrous tissue which invades the Haversian canals and displaces the contiguous bone Areas of new bone formation may be present During the proliferative stage of the lesion there is invasion by giant cells which are present in lesser extent however, than in the giant celled tumor which some consider as a later stage of development of the lesion Areas of hemorrhage and degeneration lead to the formation of cysts which may be microscopic or comprise the main part of the lesion which then is designated as a bone cyst to be discussed next

There are few symptoms associated with local osteitis fibrosa They may be the site of a pathological fracture which first brings the patient to the attention of the physician Such fractures are most common when cystic degeneration has occurred At times there may be local pain which however is not severe and is described as a dull ache Tenderness on pressure and swelling also are noted rarely

The x ray of the affected bone reveals a rarified area which is centrally placed and sharply outlined In more advanced stages there may be extension in all directions with thinning of the cortex but without any periosteal reaction or penetration of the periosteal lining Many small cyst like areas and trabeculations may be evident[66]

Bone Cysts

The bone cyst usually is found as a solitary lesion in the medullary cavity and may be secondary to an area of osteitis fibrosa giant cell tumor enchondroma, myxoma hemorrhage or other bone disorders There is often a history of trauma so that the lesion presumably often is secondary to hemorrhage[73]

The bone cysts may be contained in a distinct lining which strips easily from the bone and is filled with a fluid containing degenerated blood cells The fibrous capsule surrounding the cyst may consist of an area of osteitis fibrosa with an infiltration of giant cells

Bone cysts occur before the age of 20 and usually remain unrecognized until they become the site of a fracture However in some cases, pain may be a symptom of their presence

The term bone cyst often is applied loosely for the apparent cavitation seen in the x ray which on biopsy is found to be filled by fibrous tissue giant cells etc It should be reserved for such cases as present a true cyst with fluid contents

Benign Giant Cell Tumor

The benign giant cell tumor as already indicated is considered by some as a modified form of localized osteitis fibrosa from which it develops It is commonly found in the epiphyseal ends of the long bones especially at the condyles occasionally in the diaphysis at the site of a periosteal hematoma which resolves itself by new bone formation or rarely in the flat bones and vertebrae The tumors tend to expand the cortex but only rarely perforate the perio teum They occur at a more advanced age than localized osteitis fibrosa that is in young or middle aged adults[87] The benign giant cell tumor occurs most commonly in the distal end of the femur the proximal end of the tibia or humerus and the distal end of the radius

The giant cell tumor consists of a vascular granular tissue which is reddish with mottled white areas It is composed of fibroblastic cells round cells and numbers of giant cells In some cases one observes an intermediate appearance between osteitis fibrosa and the typical giant cell tumor which is suggestive of their common origin[4, 44]

The symptoms of the giant cell tumor consist of a dull pain or a slowly growing

tumor Fracture is less common than in the case of the bone cyst The x ray reveals an expanded tumor which is lobulated with distinct septa As the lesion advances the trabeculation tends to disappear giving the appearance of the osteolytic form of osteoclastoma Radiotherapy may cause a reappearance of the trabeculation Periosteal lipping which usually is considered as a sign of sarcoma may be observed also at times[5] It is sometimes difficult to differentiate the lesion roentgenologically from an early stage of malignant sarcoma Histologically also the giant cell tumor originally was mistaken as a form of sarcoma and erroneously designated as myeloid sarcoma, myeloma or giant cell sarcoma Its benign nature is now well established[13], although occasionally malignant transformation apparently occurs [9 103]

Differential Diagnosis of Localized Forms

A number of conditions may simulate the radiological appearance of localized forms of osteitis fibrosa It is also impossible in many cases to differentiate the various forms in which localized osteitis fibrosa manifests itself without a biopsy Giant cell tumor usually is found at the epiphyseal end of the bone, usually is somewhat denser in appearance in the x ray and occurs somewhat later in life than the purely fibrocystic lesions

Hyperparathyroidism rarely induces a solitary lesion, which, if present is always accompanied by generalized decalcification Syphilis may produce a similar lesion but may be excluded by the history, the pain which is nocturnal the presence of other stigmata of syphilis, a positive Wassermann reaction and the accompanying periostitis[94 97]

Brodie s abscess usually reveals evidence of proliferation of the bone surrounding the abscess Myxoma resembles osteitis fibrosa in the x ray, but pain which is often severe is prominent in this disorder

Large irregular circumscribed areas of osteoporosis of the cranium, which are designated as osteoporosis circumscripta cranii may be confused with fibrocystic disease[11] The condition is seen in association with Paget s disease of bone leontiasis ossea and in tumors of the jaws and brain Rarely, it occurs in association with generalized osteitis fibrosa of hyperparathyroidism

Treatment of Localized Forms

Spontaneous healing often follows the fracture of a localized bone cyst or area of osteitis fibrosa However in most cases specific treatment is necessary Since surgical treatment permits examination and definite diagnosis of the lesion this is generally advocated as the procedure of choice[16 86] On the other hand many radiologists feel that irradiation offers the method of choice arguing that this is

effective in as great a number of cases as is surgery and that it avoids the danger of a benign giant cell tumor assuming a malignant tendency which occasionally occurs[53, 83] In the case of tumors present in inaccessible sites or extremely advanced lesions radiation is preferred

Operative interference is necessary where deformity is present or fracture is imminent due to the size and location of the lesion In this case simple curettement and obliteration of the cavity may suffice to eradicate the lesion Recurrence in such cases does not occur and complete healing of the lesion ensues If the lesion is large subperiosteal resection and a full bone graft may be required Healing may be slow and in about 30 per cent of cases of osteitis fibrosa and giant cell tumor recurrence occurs In such cases a second operative removal is indicated

Although the giant cell tumor usually is benign malignant forms are encountered which result histologically from transformation of a tumor originally benign[98]

In using irradiation without biopsy to establish the diagnosis there is always the hazard of mistaking an osteolytic sarcoma for a giant cell tumor as the two bear a close resemblance roentgenographically

OSTEITIS FIBROSA GENERALISATA SECONDARY TO HYPERPARATHYROIDISM

Introduction

Skeletal changes characterized by the development of generalized osteoporosis osteitis fibrosa giant cell tumors and bone cysts are one of the striking features of hyperparathyroidism which first called attention to this disorder Indeed the lesions of osteitis fibrosa in this condition are at times so striking a part of the clinical picture that the term osteitis fibrosa generalisata has been used as synonymous with hyperparathyroidism This is undesirable since the osteodystrophy is only one manifestation of hyperparathyroidism and may be absent in well defined cases of this disorder[46] Since hyperparathyroidism is the subject of a special chapter in the Oxford Medicine (Vol III Chap XV) only the osseous lesions associated with the disorder need be considered here

Synonyms — Hyperparathyroidism von Recklinghausen s disease of bones Engel von Recklinghausen syndrome osteitis fibrosa generalisata osteose parathyroidienne (Lievre[71]) Epithelkorperchenkrankheit (Mandl[75]), parathyroid osteitis

Definition — A chronic disorder of the bones secondary to hyperparathyroidism and characterized by generalized decalcification defective ossification and the replacement of the bone by cellular fibrous tissue with the formation of benign

giant celled brown tumors and cysts which result in multiple fractures and deformities

Historical

Von Recklinghausen[95] in 1891 published his classic monograph in which he described the heterogeneous unrelated conditions designated as fibrocystic disease of bone Earlier cases of the condition had been described by Engel[30] in 1864, Langendorff in 1877 and Davies Colley in 1884 Although von Recklinghausen's name is associated with the generalized osteitis fibrosa, which is associated with hyperparathyroidism and with neurofibromatosis of the skin, he actually did not recognize the relation of the parathyroid glands to fibrocystic disease and included cases in his original report which probably belong to the forms of osteitis fibrosa disseminata now recognized as part of the syndrome designated as fibrous dysplasia of bone

Askanazy[8] in 1904 noted a tumor of the parathyroid at autopsy of a case of generalized osteitis fibrosa but failed to relate the two conditions Three years later Erdheim[31] noted that osteomalacia was accompanied by parathyroid enlargement which he considered to be of the same nature as the enlargement accompanying osteitis fibrosa generalisata Because of his authoritative opinion Erdheim's view of the relation of the parathyroid glands to generalized fibrocystic disease was followed for two decades As early as 1915 however, Schlagenhaufer suggested the operative removal of parathyroid tumors and in 1922 Weil subjected a case to irradiation with the claim of good results

Mandl's[7] successful extirpation in 1926 of a parathyroid tumor on a patient suffering from osteitis fibrosa cystica and the subsequent studies on the function of the parathyroid glands in regulating calcium metabolism led to the association of osteitis fibrosa generalisata and hyperparathyroidism Following Mandl's classic report instances of adenoma of the parathyroids accompanied by osteitis fibrosa cystica accumulated rapidly so that in 1930 Ask Upmark could report 14 operated cases The following year there were 30 and by 1938 Mandl had collected ~00 cases from the literature For a time confusion existed because of lack of exactness in diagnosis and a failure to differentiate other conditions causing hypercalcemia

It soon became clear also that the skeletal changes were only one aspect of the clinical picture and that only a minority of the patients suffering from hyperparathyroidism present the classical picture of osteitis fibrosa generalisata

Incidence

Generalized osteitis fibrosa cystica secondary to hyperparathyroidism is a relatively rare condition[46] It is more frequent in women than in men, being ob-

served two to three times as often in the former as in the latter In women it is most common in the fifth decade of life in men during the fourth decade It may however occur at any age In Landon s case of a 2½ year-old boy lesions had appeared first at 6 months of age Anspach and Clifton[7] reported 12 cases in children varying from 2½ to 17 years of age There is no definite evidence of any familial tendency to the disorder although cases in siblings have been reported[45]

Pathogenesis

The skeletal changes are secondary to an overproduction of parathyroid hormone which results in an excessive loss of calcium phosphate from the body and the bones The mechanism of this action is not entirely clear It apparently is not due solely to action on the kidney as was formerly claimed[63 64 104 109] The degree to which the bones are affected may be determined to a large extent by the amount of lime salts ingested by the patient This would account for the fact that in some cases the osseous lesions may be minimal and limited to osteoporosis while other abnormalities such as renal lithiasis and insufficiency bring the patient to the attention of the physician It has been estimated that about 40 per cent of all patients with hyperparathyroidism lack distinctive lesions in the bones Emphasis on the skeletal defects has resulted in recognition of the disorder in patients manifesting these and it is only in recent years that attention has been focused on other clinical features of the disorder Of the 5 patients with hyperparathyroidism proven at operation encountered recently by the author classical bone deformities were present in one and a pathological fracture of a solitary bone cyst in another The other 3 presented recurrent renal calculi anemia and renal insufficiency secondary to long standing lithiasis and renal infection without striking lesions of the skeleton

As in the case of other neoplasia the cause of the hyperparathyroidism is obscure It has been attributed to insufficient sunlight and vitamin D deficiency because of the fact that 126 of the first 135 reported cases appeared in northern countries[51] However this is improbable As interest and knowledge of the disease increases it is being recognized throughout the world

Pathology

Bones

In the generalized form of osteitis fibrosa cystica associated with hyperparathyroidism there are multiple areas of rarefaction of the bones with cyst formation The decalcification of the bone involves the entire skeleton which is of fundamental importance in differentiating this condition from other bone disorders in which

there may be diffuse involvement of one or more bones The widespread osteoporosis leads to softening of the bone with marked deformities as in the skeleton shown in Fig 24

The medullary canal is increased in size and becomes cystic with the cavity filled with a gelatinous or serous material The cortex is thinned, the Haversian canals are enlarged and replaced by fibrous tissue The fibrous tissue, being poorly vascularized undergoes cystic degeneration Osteoblastic activity may be evident with the production of a poorly calcified osteoid tissue Other areas reveal many multinucleated osteoclasts

Where pathological fractures have occurred there is excessive callus formation with poorly formed osteoid tissue

The bone changes in osteitis fibrosa may consist only of slight decalcification with only a few cystic areas In other cases there may be marked general changes with spindle expansion of the rarified bones and the formation of many cysts and brown tumors In advanced cases multiple fractures and infractions lead to grotesque deformities of the skeleton Fibrous tumors of the jaws and gums epulis, are observed frequently[90]

Histologically one observes lacunar resorption with fibrous displacement of the normal osseous architecture The fibrous tissue is cellular and contains many young and matured fibroblasts It is relatively avascular and contains a large amount of collagen with many spindle cells containing pale staining nuclei (Fig 25) There may be also some lymphocytic infiltration with occasional nests of large osteoclasts

Osteoblastic activity is almost absent, although occasionally a small deposit of poorly formed bone or cartilage may be noted The trabeculae are faint with little calcium present

The compact part of the Haversian canals are converted to irregular spaces in the walls of which cavities appear which contain giant cells and osteoclasts The spaces themselves contain loose vascular, connective tissue Similar changes are seen in the spongiosa where the bone marrow is penetrated by loose connective tissue The numerous thin walled vessels are prone to hemorrhage which results in the formation of hemosiderin which stains the tissue brown There are thus formed large or small masses the brown tumors Secondary liquefaction converts these to cysts Simultaneously with this resorption there occurs new bone formation in the newly formed connective tissue which however, lags behind the destructive process As a consequence the bones at multiple points develop cystic enlargements which often are enclosed in a paper thin cortex At an early stage of the process there is only an increased porosity of the bone which is replaced in the Haversian canals by connective tissue The marrow is scarcely affected, and no brown tumors or cysts are to be found in the bone marrow at this stage of the disease[60]



FIG 24 Deformities of the skeleton in generalized osteitis fibrosa skeleton Reproduced from the original report of von Recklinghausen It is questionable if this represents an instance of hyperparathyroidism as usually assumed or one of osteitis fibrosa disseminata

Parathyroid Glands

The excessive production of hormone in hyperparathyroidism may be associated with three types of changes in the parathyroid glands, 1) hyperplasia of all the glands 2) adenoma of one or more glands or 3) malignancy of the glands[19]



FIG 25 The microscopic appearance of the tissue in a case of osteitis fibrosa secondary to hyperparathyroidism The marrow has been replaced by fibrous tissue of the usual spindle cell variety

Hyperplasia of the glands may be primary or secondary[99] The latter refers to the enlargement seen in a number of conditions associated with abnormalities in calcium and phosphorus metabolism particularly renal insufficiency and osteomalacia[54] The enlargement of the parathyroids in these conditions is secondary to the primary disease In primary parathyroid hyperplasia overproduction of hormone induces changes in the skeleton and other alterations in the body economy similar to that observed when these glands are neoplastic It is responsible for hyperparathyroidism in probably less than 10 per cent of all cases in which this disorder is encountered The glands are uniformly enlarged brownish in color and consist of the water clear Wasserhelle type of cell They have a broken irregular surface with frequent projections[57 108]

Neoplasia in the form of an adenoma of one parathyroid gland rarely several is responsible for most cases of hyperparathyroidism The uninvolved glands under such conditions are depressed and undergo atrophy of disuse An atrophied gland when encountered at operation is evidence to the surgeon of the presence of a neoplastic gland Adenomas have a smooth surface and like hyperplastic glands are brownish in color and consist usually of chief cells Glands which have undergone secondary hyperplasia retain the normal brownish yellow color of the normal gland This is of importance to the surgeon for if renal insufficiency has been induced as a result of an adenoma of the one parathyroid the remaining glands may become secondarily enlarged and be mistaken for an adenoma at operation[24, 113]

It was believed formerly that all instances of hyperparathyroidism were due to adenoma or hyperplasia of the glands and that malignancy did not occur However several well-established cases are on record in which the cytological appearance of the glands as well as their recurrence and metastases proved their carcinomatous nature[1, 40, 77, 90] Alexander and his co-workers[6] conclude that 92 8 per cent of their series of 14 cases were malignant although exception might be taken to the histological criteria upon which this conclusion was based in some of their cases

Other Changes

In addition to the changes in the bones and parathyroids the most striking pathological alteration occurs in the kidneys The deposition of lime salts leads to the formation of kidney stones and calcification of the renal pyramids This extra osseous calcification often is evident in the x ray Other parenchymatous organs may be similarly affected with involvement of the small blood vessels in the lower extremities subacromial bursa and other areas[17, 3, 46]

SYMPTOMS

Although all patients suffering from hyperparathyroidism undergo the changes of osteitis fibrosa these are often of an insufficient degree to elicit symptoms referable to the skeletal system Renal calculi often first bring the patient to the attention of the physician and hyperparathyroidism should always be excluded as a possible cause of this disorder particularly when the involvement is bilateral or recurrent[68]

The most consistent early symptoms are weakness and fatiguability Other symptoms are loss of weight anorexia constipation and gastrointestinal disturbances The latter are particularly common in cases of acute hyperparathyroidism Fever which may occur periodically is not an unusual symptom It is

Parathyroid Glands

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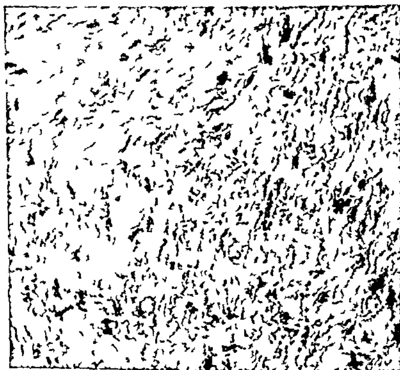


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FIG 27 Generalized osteitis fibrosa cystica of the pelvis and femur in a 51 year-old man suffering from hyperathyroidism

ity[19] Despite the generalized decalcification the teeth retain their structure except for the loss of the dura lamina which is evident at an early stage of the disorder[100 10?]

usually of the undulating type Polydipsia and polyuria are observed commonly[33] Anemia due to replacement of the bone marrow may be the presenting symptom[79]

The symptoms related to the skeletal system are pain referable to the bones and joints of the extremities and spine pathological fracture, kyphosis scoliosis and deformities of the thorax and long bones A disturbance in gait, which becomes waddling is observed early in the disease Later the patient is unable to walk[84 111]

X ray Findings

Roentgenologically the characteristic changes consist of a coarsely granular osteoporosis due to the loss of lime salts and replacement by fibrous or cystic tissue (Fig 26) The long bones present a broadening or expansion with thinning



Fig 26 The skull in hyperparathyroidism Showing the granular appearance and generalized decalcification in a 48 year old man from whom an adenoma of the parathyroid subsequently was removed

of the cortex where cysts are present (Fig 27) and deformities due to collapse of the supporting structures The texture of the bone is rarified and trabeculated and between the areas of cysts the bone shadow appears lacking its normal den

associated with it[7,47] Its differential diagnosis has been discussed elsewhere in this chapter

In the accompanying table (Table I) are summarized the principal differential findings in hyperparathyroidism and other disorders of the bone in which osteitis fibrosa is encountered or in which this condition is simulated in the x ray

Treatment

Having established the diagnosis of hyperparathyroidism exploration and removal of the affected parathyroids is indicated Should tumors or generalized hyperplasia of the glands not be found in the neck they should be sought for elsewhere In a good proportion of the cases the position of the affected gland is atypical[1,3,24] being found between the esophagus and trachea or most often in the superior mediastinum

The parathyroids are relatively insensitive to the x ray and it is the general concensus of opinion that irradiation is of no value in the disease However amelioration of generalized osteitis fibrosa by irradiation of the neck has been claimed[19,76,87] In any case the relative insensitivity of the glands and the possibility of malignancy renders irradiation an undesirable form of therapy except in patients refusing operation

Care must be taken to avoid tetany which may prove fatal following removal of the neoplastic glands This is particularly apt to occur in cases where there is marked decalcification Partial resection of the tumor in such cases has been advocated The patient should be observed carefully and any tendency to tetany as revealed by a positive Chvostek or Trousseau sign be counteracted by the usual measures[46]

In the case of diffuse hyperplasia of all the glands at least three of the four should be extirpated with part of the fourth Fragments of the latter may be transplanted into pockets of the abdominal or sternocleidomastoid muscles in which position they are readily accessible should their removal be subsequently desirable

Following removal of the offending gland there is a prompt return of the blood chemical changes to normal and healing of the osseous lesions usually occurs within a few months[74] There may be great reduction in the size of the cysts and tumors with healing of fractures Deformities however are not spontaneously corrected and may require orthopedic intervention

CONGENITAL DISORDERS ASSOCIATED WITH OSTEITIS FIBROSA

Disseminated lesions of osteitis fibrosa may occur as part of certain congenital disorders particularly in association with fibrous dysplasia of bone and von Reck

Although all the bones are involved, the degree of involvement in different areas varies The long tubular bones the pelvis skull, jaw and ribs are most affected The diaphyses of the bones show the greatest involvement Loss of the mineral elements results in softening and deformity particularly of the bones which are subjected to stress

Although not pathognomonic, the diffuse involvement of the skeleton and the presence of multiple cystic areas gives an x ray picture which is unlike that seen in other disorders[93 96]

Diagnosis

The recognition of hyperparathyroidism is not difficult for, in addition to the characteristic changes in the bones as revealed in the x ray, there are pathognomonic changes in the chemical composition of the blood[5 15 37 49 67] as discussed in the chapter on hyperparathyroidism The principal errors arise from a failure to exclude other conditions in which there is decalcification of the skeleton accompanied by hypercalcemia[1 43 80]

Tumors of the parathyroid are only rarely palpable although in a few cases large tumors weighing 38 to 100 grams, have been found Occasionally calcification of the tumor allows its detection in the x ray In other cases deviation of the trachea or compression of the esophagus as revealed by the x ray may lead to demonstration of a tumor

Among the conditions which have been confused most often with hyperparathyroidism are polyostotic fibrous dysplasia or osteitis fibrosa disseminata[39], as it has also been designated and metastatic lesions of the bones[10] In both of these conditions the uninvolved parts of the skeleton do not show the decalcification which in hyperparathyroidism is uniform The blood calcium and phosphate are normal in fibrous dysplasia, although the phosphatase may be moderately elevated In metastatic carcinoma the blood calcium may be elevated but the inorganic phosphate is not diminished as in hyperparathyroidism In questionable cases a biopsy will establish the diagnosis in case of metastases but this is rarely needed

In hyperthyroidism one encounters osteoporosis by osteoclastic resorption which is localized in parts of the skeleton exposed to activity and can only be seen on microscopic section rarely in the x ray Very rarely are cysts formed which resemble osteitis fibrosa generalisata Calcium and phosphorus excretion are increased but the blood levels remain normal and the phosphatase is only moderately increased[46]

Generalized xanthomatosis may be differentiated from osteitis fibrosa generalisata by the x ray and biochemical findings[9]

Paget s disease sometimes is confused with hyperparathyroidism and may be

linghausen s neurofibromatosis In the former it is the principal manifestation of the disorder in the latter it is one of the less outstanding features

Fibrous Dysplasia of Bone

This condition has only recently been recognized as a distinct clinical entity involving fibrous displacement of bone It is discussed in detail in part VIII of this chapter hence only the relation of the disorder to osteitis fibrosa will be considered here

Fibrous dysplasia of bone may occur either as a single lesion or in a more disseminated form[70] For this reason it has been designated also as osteitis fibrosa disseminata to differentiate it from osteitis fibrosa generalisata the name which is commonly applied to the skeletal manifestations of hyperparathyroidism Since the involvement usually is regional or unilateral the terms regional osteitis fibrosa and osteodystrophia fibrosa unilateralis have been applied also to the disorder[36 28 104]

In Fig 28 is reproduced a typical example of the lesions as seen in the x ray Although indistinguishable from osteitis fibrosa localisata when occurring as an isolated lesion the disorder tends to be more disseminated with a unilateral distribution When the lesion appears in the skull there is deposition of new bone particularly at the base which when present also aids in the diagnosis[3] Grossly and histologically the lesions also show some differences from the ordinary case of osteitis fibrosa Small areas of bone usually are present which give the mass a gritty feeling and under the miscroscope the fibers are arranged in whorls Clinically the bone lesions sometimes are accompanied by pigmented areas in the skin and endocrine disturbances particularly precocity (Albright s syndrome)

Neurofibromatosis

Von Recklinghausen s neurofibromatosis originally was considered as a disorder of the peripheral nerves alone especially of the cutaneous filaments However in addition to the multiple oft nodules of the skin molluscum fibrosum and the subcutaneous neurofibromata so often seen in the disorder pigmentary changes in the skin and bone lesions are not uncommon The latter may comprise areas of cystic degeneration as well as other derangements in the bone structure which may lead to enlargement overgrowth and deformity particularly scoliosis or other changes in the vertebral column General osteoporosis and decalcification of the pelvis may occur Abnormalities of growth and the so-called subperiosteal cyst are common The latter are formed by invasion of the bone by a neurofibroma the osteogenetic periosteum covering the tumor forming a shell of bone around it which gives it a pseudo-cystic appearance The involvement varies

TABLE I

DIFFERENTIATION OF DISORDERS OF BONE CHARACTERIZED BY OR SIMULATING OSTEITIS FIBROSA

	Distribution of Lesions	X ray Findings	Blood Chemistry	Biopsy
Hyperparathyroidism	Generalized	Rarefaction and thinning of cortical bone multiple cystic lesions	High calcium and phosphatase low phosphate	Lacunar resorption with fibrous displacement and cystic degeneration
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Osteonephropathy	Generalized	Osteoporosis and mottling calcification of kidneys and smaller blood vessels	Normal or low calcium evidence of renal insufficiency	Lacunar resorption with replacement by fibrous tissue generalized osteoporosis
Thyrotoxicosis	Generalized	Osteoporosis	Normal	Depletion of calcium from trabeculae
Leontiasis ossea	Confined to skull	Osteoporosis circumscripta surrounded by thick eburnated bone	Normal	Extreme osteoblastic activity
Xanthomatosis	Generalized but particularly in skull	Localized rarefaction	Normal	Characteristic foam cell
Multiple myeloma	Limited to skull spine ribs clavicle long bones	Moth eaten punched-out areas	Calcium only elevated hyperglobulinemia	Presence of typical tumor cells
Metastatic carcinoma	May affect any bones usually localized	Localized defects with osteoblastic tendency in some cases	Calcium may be normal or elevated	Presence of tumor cells

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Leontiasis ossea	Confined to skull	Osteoporosis circumscripta surrounded by thick eburnated bone	Normal	Extreme osteoblastic activity
Xanthomatosis	Generalized but particularly in skull	Localized rarefaction	Normal	Characteristic foam cell
Multiple myeloma	Limited to skull spine ribs clavicle long bones	Moth eaten punched-out areas	Calcium only elevated hyperglobulinemia	Presence of typical tumor cells
Metastatic carcinoma	May affect any bones usually localized	Localized defects with osteoblastic tendency in some cases	Calcium may be normal or elevated	Presence of tumor cells

from slight irregularity of periosteal or cortical structure to large tumors projecting from the surface of the bone or embedded within it as a cyst like cavity Histological examination reveals a structure similar to the tumors seen in the skin Radiologically they resemble those seen in osteitis fibrosa cystica giant cell tumor and xanthomatosis Cystic changes in the skull are particularly common with thinning and defects of the cranium

Thannhauser[106] in a recent survey of the literature on neurofibromatosis and osteitis fibrosa disseminata or polyostotic fibrous dysplasia has come to the conclusion that both disorders have a common congenital origin and that the latter condition should be considered as a form of von Recklinghausen s neurofibromatosis without involvement of the peripheral nerves This view is supported by the similarity in the appearance of the skeletal lesions[107] as well as by the fact that endocrine disturbances and pigmentation of the skin occur in both disorders

OTHER DISORDERS ASSOCIATED WITH FIBROCYSTIC DISEASE OF BONE

Since the displacement of bone by fibrous tissue represents a non specific reaction to local osteoporosis it is not unexpected that the condition should be associated with a number of disorders in which decalcification occurs The most common disorder in which this occurs is renal insufficiency Not only do the changes in the bones under these conditions resemble those seen in hyperparathyroidism but there may also be a secondary enlargement of the parathyroid glands

OSTEONEPHROPATHY

Structural changes characteristic of osteitis fibrosa may occur in the course of prolonged renal insufficiency However one does not observe in this condition the widespread cystic changes seen in the disorders already discussed Skeletal disturbances are particularly striking in congenital renal disorders since these interfere with growth of the bones at the period of their greatest development The condition observed leads to deformity and dwarfism (see Dwarfism Vol III Chap XIX in Oxford Medicine) and has been designated as renal rickets The term osteonephropathy more accurately describes the condition and is less misleading It may be applied to all abnormalities of the bones secondary to renal disturbances[4, 85]

Osteonephropathy or renal osteitis fibrosa as it is also designated is seen in its more florid development in congenital forms of osteonephropathy but may occur also in adults dying of renal insufficiency of various types[43] It is observed more frequently in chronic glomerulonephritis or pyelonephritis than in chronic vascular nephritis[34] In osteonephropathy the most prominent finding is the



Fig 28 Regional osteitis fibrosa (polyostotic fibrous dysplasia) involving the long bones of the arm in a 14 year old boy The right humerus (left photograph) is markedly involved and was the site of two pathological fractures which have healed There is thinning of the cortex of the entire shaft a decrease in density and fusiform swelling The photograph on the right shows involvement of the ulna of the other arm with thinning of the cortex in the upper third of the shaft and only slight involvement of the lower end of the humerus on this side

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presence of excessive osteoid tissue as in osteomalacia The changes of osteitis fibrosa are encountered less frequently Their occurrence may be looked upon as a reaction to the osteoporosis resulting from the acidosis[6, 63] of renal insufficiency and probably not to the compensatory hyperplasia of the parathyroids induced by this process although such hyperplasia occurs and has led to erroneously attributing the condition to hyperparathyroidism[61]

Hyperparathyroidism is rare in childhood[46], and many of the cases diagnosed as juvenile hyperparathyroidism are instances of osteonephropathy secondary to congenital renal disease[83] In the adult the differentiation of the two conditions is rendered difficult by the fact that bilateral renal calculi and pyelonephritis often complicate hyperparathyroidism The biochemical findings of the blood are important in establishing the diagnosis

Treatment of osteonephropathy is directed towards overcoming the renal insufficiency and correcting the abnormal calcium metabolism There is no reason to believe that removal of the enlarged parathyroid glands would prove of value, since this is a compensatory reaction rather than a cause of the osseous lesions

Hyperthyroidism

Hyperthyroidism by interfering with the normal absorption of calcium may result in decalcification of the bones and the production of isolated lesions of osteitis fibrosa[58] Similar effects may occur in sprue osteomalacia and other conditions associated with osteoporosis However, only isolated cystic areas usually are present in these conditions as well as in osteonephropathy, which differentiate these conditions from the disseminated or generalized forms described in the earlier sections of this chapter

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Part XI

MULTIPLE MYELOMA

Introduction

Synonyms — Kahler's or Huppert's disease myelopathic or Bence Jones albumosuria lymphadenia ossea plasmocytoma myeloma plasma cell myeloma multiple aleukemic myelocytoma plasmocytic leukemia

The terms plasmoma and plasmocytoma are applied to the extra osseous tumors *which are now recognized as basically of the same pathogenesis as multiple* myeloma Myelocytoma lymphoblastoma and erythroblastoma have been used to designate cases of the disease in which the cell type resembles the myelocyte lymphoblast and erythroblast respectively rather than the plasma cell which i found in the majority of the tumors

Definition — Multiple myeloma is a primary specific malignant disorder of the bone marrow which gives rise to a diversity of symptoms and findings in the bones central nervous system blood kidneys and other tissues It is a tumor arising probably from a single cell type which appears in several forms but which most commonly resembles the plasma cell Although usually characterized by multiple foci of origin in the bone marrow it appears occasionally as an isolated lesion may have an extra osseous site of origin or may be generalized (myelomatosis)

Historical

McIntyre[79] in 1850 reported the first authentic case of multiple myeloma in a patient seen in consultation with Bence Jones[10] who discovered the characteristic protein in the urine which has since been designated by his name and by Dalrymple[31] who made the first microscopic examination of the ribs of this same patient Bence Jones and his colleagues described the disease as a softening and fragility of the bones mollities ossium et fragilitas and administered alum in an attempt to check the exhausting excretion of animal matter

Only 3 probable cases of the disorder were described between 1848 and 1873 when Rustizky[103] in von Recklinghausen s laboratory made a careful histological tudy of the disease and demonstrated the existence of multiple tumors of proliferating bone marrow elements Kahler[65] in 1889 first called attention to the coexistence of Bence Jones protein in the urine and the disorder of the bones

described by Rustizky and emphasized the other features of the syndrome, fragility pain and deformity of the bones and cachexia The disorder has, therefore received the eponym, Kahler's disease

Wright[135] in 1900 first called attention to the morphological similarity of the myeloma and plasma cells, and Christian[27] in 1907 pointed out that despite the variations between the cells in different patients there was a fundamental resemblance between them

Geschickter and Copeland s excellent review[43 44] of 425 cases in 1927 and that of Magnus Levy[77] in 1938 as well as numerous other reports and reviews of the subject have described the clinical features of the disorder and clarified the nosological relationship of the diverse forms in which it is manifested[1 5 1 3 35 45 5 57 59 68 1 4]

Incidence

Multiple myeloma is a relatively rare disorder Symmers[1 0] found only 3 cases in 4 000 autopsies while Geschickter and Copeland[43] observed 4 cases in 9 000 autopsies It constitutes only about 0 03 per cent of all malignancies[44]

Age — Multiple myeloma is primarily a disorder of later life As with other malignancies the greatest incidence is between the ages of 40 and 70 with a mean average about 55 years[43] However verified cases in young patients have been reported[134] Some of the reported cases in children probably are not instances of this disease, but at least 8 well authenticated cases are on record[11 46 61 138] Magnus Levy[77] collected 7 cases in children and Slavens[114] reported a case proved by autopsy in a boy 4 years of age

Sex — Multiple myeloma occurs twice as frequently in the male as in the female[43]

There is no evidence to indicate any hereditary or familial tendency, nor does trauma infection climate race or social status appear to be of any significance in its distribution[80 110 1 4 131]

Pathogenesis

Multiple myeloma has been variously considered as 1) a local bone tumor[43] 2) a local tumor of reticuloendothelial origin[56] 3) a diffuse proliferation of the reticuloendothelial system[35] or 4) a form (aleukemic) of leukemia[116] The available evidence would indicate that multiple myeloma is to be regarded primarily as a disorder of the reticuloendothelial system analagous in its behavior as shall be shown in the next section to the various disorders of the lymphoid tissue Multiple myeloma is not necessarily confined to the bone marrow generalized diffuse myelomata as well as entirely extra osseous involvements occur In fact at autopsy even in the typical case one finds usually a proliferative process involving

the entire reticuloendothelial system particularly in the spleen and lymph nodes[53 70]

The reticuloendothelial origin of the disorder accounts for those instances of myeloma in which infiltration of the spleen liver and lymph nodes present the predominant finding at autopsy as well as those cases which are primary in the naso pharynx, conjunctiva testis or other extra osseous sites

The Myeloma Cell

There has been much disagreement regarding the nature of the cell involved in multiple myeloma The characteristic cell in most cases (Fig 29) resembles the ordinary plasma cell which is found normally in the mucous membranes



Fig 29 Sternal Marrow in Multiple Myeloma The appearance of the marrow as obtained by sternal biopsy in a case of multiple myeloma showing the large number of myeloma cells (of the plasma type) and autohemagglutination characteristic of the disease (Courtesy Dr J M Hill)

interstitial and lymphoid tissue and rarely in the blood It is observed in chronic inflammatory tissue and may constitute 10 per cent or more of the leukocytes of the blood in rubella and to a lesser extent in other infections (scarlatina measle chickenpox etc)

The cells observed in patients with multiple myeloma vary considerably although as shown by Christian [7] there is a well defined resemblance between members of the series The various cell types have been designated depending on

their appearance as lymphocytes, lymphoblasts myelocytes, myeloblasts erythroblasts and plasma cells[77] Ewing[35] classified the myeloma as 1) plasmocytoma, 2) erythroblastoma 3) lymphoblastoma and 4) myelocytoma depending on the characteristic appearance of the predominant cell However, in certain cases one finds cell types which defy classification into one of these four groups

It has been assumed by many that the different cell types represent cells of diverse origin However it is more likely that all the cell types originate from a single primordial cell and are of the same basic type in various stages of differentiation Multiple myeloma according to this view is a pathological entity which manifests itself by variations in cell type It may be designated as plasmocytic, myeloblastic or erythroblastic depending upon the superficial appearance of the predominant cell type but all forms are fundamentally of the same origin

The most common cell type is the so called 'plasmocyte' which was encountered in 207 of a total of 311 cases collected by Atkinson[1] Of the remaining 104 cases 27 were described as 'myeloblastic", 24 as "myelocytic", 16 as 'lymphocytic 5 as erythroblastic' 28 as 'mixed' and 4 as doubtful

Although it is generally believed that the normal plasma cell is of lymphocytic origin it is probable that the plasma" cell of multiple myeloma is of myeloid origin[3] The plasma cell, which occurs in multiple myeloma, usually is about 15 to 30 micra in diameter with an eccentric nucleus, 5 to 7 micra in diameter The latter contains one or two nucleoli The chromatin is not arranged in spoke like fashion as in the normal plasma cell, and the cytoplasm is bright blue rather than blue green as in the latter The presence of a clear perinuclear zone, which is characteristic of the plasma cell also is unusual in myeloma, nor does the cytoplasm take the specific plasma cell stain or show the oxidase reaction[1 8]

Because of the differences just outlined it is preferable to speak of the 'myeloma' cell rather than the plasma cell as constituting the cell type in multiple myeloma Although superficially resembling the normal plasma cell there are certain differences between the latter and the plasma' cell found in cases of multiple myeloma and the two may not be identical They differ in size, staining reaction and as regards their finer cytological characteristics

In many cases the predominant cell as already indicated, resembles the myeloblast erythroblast or lymphoblast rather than the plasma cell and all transitional forms between these and plasma cells may be found All of them are best referred to as variants of the myeloma cell which may follow any of its original potentialities of differentiation along myeloid lines

As is to be expected there is some correlation between the cell type in different forms of myeloma and their degree of malignancy Thus of the 7 cases of multiple myeloma reported in children by Magnus Levy[77] 4 were of the myeloblastic cell type The disorder in the child appears to express itself in a more malignant and less differentiated cell type

Relation of Multiple Myeloma to Leukemia

Multiple myeloma may be regarded as a disease of the reticuloendothelial component of the blood forming organs analogous to the leukemias with predominant participation of the bone marrow but involving also other blood forming tissues Although usually aleukemic in nature the disorder may manifest itself by the appearance of the characteristic myeloma cells in the blood giving rise to what is usually designated as plasmocytic leukemia According to this view plasma cell leukemia may be classified also as a variant of multiple myeloma Such a classification is particularly appropriate in those cases in which there is a nodular involvement of the marrow by plasma cells with destruction of bones a condition sometimes referred to as myeloma cell leukemia[63 86 91]

One of the principal difficulties encountered in attempting to classify multiple myeloma as a disorder of the hemopoietic system arose from the assumption that the myeloma cell is of lymphocytic origin Such an assumption would make it necessary to classify multiple myeloma as a form of lymphoma which presents many incongruities On the other hand if the myeloma cell be considered as of reticuloendothelial origin it is possible to explain the various manifestations of the disorder and at the same time account for the resemblance as regards many of its clinical features to leukemia

The diffuse nature of multiple myeloma as it is most commonly observed suggests a relationship to leukemia[36 47] There is a good analogy between the various clinical forms in which multiple myeloma may appear and the corresponding disorders of the lymphocyte Thus one encounters solitary relatively benign tumors within the bone marrow or in extra-osseous sites plasmocytomas of the naso-pharynx or plasmomas of the conjunctiva which may be considered as analogues of the giant folliculoma encountered in the lymphatic system In the more malignant stages one encounters involvement of one or more bones with or without extra osseous lesions which may be compared to lymphosarcoma Diffuse myelomatosis is analogous to so-called aleukemic lymphatic leukemia while plasmocytic leukemia corresponds to lymphatic leukemia In plasmocytic leukemia the involvement of the marrow has broken through the blood barrier and as many as 70 per cent of the leucocytes may consist of myeloma cells[7 77 86]

The above described hypothesis which unifies the diverse forms in which myeloma appears is supported by the existence of analogous conditions in the various abnormalities of the lymphoid tissue That the same pathological process may express itself in various forms has been demonstrated experimentally by Furth[41] who showed that either a localized form of myeloma or a myeloid leukemia can be induced in susceptible mice depending on the route of administration of the transmissible strain[6] That varying degrees of anaplasia should be associated with a single cell is generally accepted

Pathology

The group of disorders, which are related to multiple myeloma, differ widely in their pathological as well as their clinical manifestations They may be broadly classified into 1) the classical type of multiple myeloma in which there is multiple involvement of many areas of the bone marrow, 2) the isolated myeloma in which only one area in a single bone is affected 3) generalized myelomatosis in which all hemopoietic tissues are extensively involved, 4) extra osseous myeloma in which the lesions do not appear in the bones or affect these structures only secondarily Clinically the disorder varies from the localized and relatively benign condition seen in plasmoma of the conjunctiva to the widespread and rapidly fatal generalized myelomatosis

Bones

The bones most commonly affected particularly in early stages of the disease are the spine and ribs The femora and skull are the next most frequent sites affected, and in moderately advanced cases the typical changes occurring in the calvarium are characteristic The clavicles and humerus are the third sites most commonly affected[43] The disease makes its first appearance in one of the above mentioned bones and attention may be drawn to it by a tumor fracture or pain associated with a lesion in the spine ribs femur, mandible, clavicle, humerus or sternum

The tumors vary in size from pin point to an orange Occasionally there is a diffuse involvement of all the marrow, myelomatosis without evidence of tumor formation

Biopsy of the tumor tissue reveals a dark red or grayish red gelatinous mass which on microscopic examination is found to consist of the characteristic "myeloma" cell[130] Histologically the tumors appear as cords of typical plasma cells arranged between delicate connective tissue and capillary stalks with little or no stroma The tumor cells when of the plasma cell type are characterized by their eccentric nucleus a scanty cytoplasm which is markedly basophilic and the absence of the spoke like arrangement of chromatin seen in the normal plasma cell (Fig 29) There is also often seen a smaller cell resembling an immature lymphocyte The myeloma cells contain characteristic crystals which are believed to represent the Bence Jones protein[117] The degree of malignancy of the cells may be gauged by their content of these crystalloid inclusions[136 137]

The myeloma cells show many variations in structure The nucleus usually stains deep purple with the chromatin arranged in coarse particles The cytoplasm stains pale blue and often is vacuolated The chromatin of the nucleus often lacks the coarse radial arrangement the perinuclear space (Hof) and characteristic stain seen in the normal plasma cell

Solitary Myeloma

About 50 cases are on record in which instead of multiple involvement of the bones only a single lesion has been found at autopsy[34 4] Patients in whom the disease is localized may remain well for many years after local treatment but in most cases the local lesion soon undergoes the typical multiple spread In some cases the localization of the tumor undoubtedly is apparent rather than real for sternal puncture will reveal the typical myelomatous cells It is probable that in these cases the disease has undergone marked progression in one rather than in many sites but that it nevertheless is widespread in distribution In the same category may be placed those cases in which study of the blood and sternal marrow reveals a typical picture suggestive of multiple myeloma but in which x ray of the bones fails to reveal the presence of anything except moderate decalcification suggestive of senile osteoporosis Only after some months will the typical x ray findings become manifest

Single myelomata occur usually in the long and flat bones where they produce tumors of osteolytic type without much tendency to spontaneous fracture The multiple osteolytic tumors of the marrow destroy the bone from within and lead to pontaneous fracture In both types there are no true metastases although the invasiveness approaches at times the sarcoma type and sarcomatous changes with metastases may take place

Microscopically the cells of these tumors show considerable variation but tend to be uniform in any given case The most common type is the plasma cell type Others show variation in cell size and staining characteristics Such variation in size is an indication of greater malignancy

The tumors of multiple myeloma in addition to their presence in the bones are confined chiefly to the hemopoietic tissues It is unlikely that these represent metastases as many believe but rather autochthonous tumor formation in the reticuloendothelium of these tissues The latter view is supported by the occurrence of the extra osseous myeloma in the lymph nodes liver spleen and tonsils which may be the only obvious site of involvement with minimal changes in the bones Very rarely metastases occur in the thyroid adrenals lungs and ovaries The rarity of metastasis to the lungs in contrast to other tumors of the bone is helpful in the diagnosis[43]

Blood

The blood picture in multiple myeloma is variable[40] A moderate degree of anemia due to displacement of hematopoietic tissue by the tumor with a relatively normal white blood count usually is present In the late stages of the disease the added effect of cachexia leads to marked secondary anemia The red

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desquamation such as one sees in intoxications by metals there being only minor epithelial damage[38]

The renal damage observed in multiple myeloma has been attributed to the excretion of the Bence Jones protein but it is unlikely that this results from a specific toxicity since no glomerular, epithelial or capillary injury is observed In all cases of prolonged Bence Jones proteinuria there develops eventually a disturbance in function of the kidney which is directly due to the excretion of the protein which causes tubular obstruction[59] The casts observed in the tubules in patients manifesting Bence Jones proteinuria have a constant structure and appear to provoke a local foreign body reaction due to obstruction of the tubular lumina This leads to secondary changes in the kidney with replacement of damaged nephrons by scar tissue

The excretion of Bence Jones protein by the kidney produces significant anatomical injury only when excreted in large enough amounts and for a sufficiently long period to induce obstruction of the tubules In the presence of a moderate persistent elevation in the blood non protein nitrogen a decrease in urea clearance and pronounced Bence Jones proteinuria one can predict the finding of the characteristic multiple myeloma kidney at autopsy with its specific lesions However renal insufficiency in some instances is due to arteriosclerosis which is common in the age group afflicted by the disorder In other cases it is caused by pyelonephritis secondary to compression of the spinal cord or to prostatic hypertrophy The cortical atrophy is secondary to obstructive effects it does not seem to be a nephrotic contracted kidney The accumulation of a highly concentrated protein solution in the glomerular capillaries occasionally may contribute also to the condition[9, 33]

An elevation of the blood pressure secondary to renal damage is uncommon

Extra medullary Plasma Cell Tumors

In addition to the characteristic tumors of the bone marrow which constitute the majority of cases of multiple myeloma one also observes extra medullary plasma cell tumors Since the liver spleen and lymph nodes are hematopoietic tissues in the embryo it is not surprising that myeloblastic tumors might arise in these tissues independently of the bone marrow

The plasmocytomata which arise in extra osseous sites of the body vary from benign to highly malignant types The site of their localization and gross appearance appear to be a more reliable criterion of their malignancy than their histological structure Although remaining localized and noncancerous for many years the process without any apparent change in the appearance of the cells may become generalized

Hellwig[56] has reviewed and analyzed 127 cases of extra medullary plasmocy

blood count in most cases varies between 2 and 3.5 million, but in about one quarter of the cases a count of 4 million or more may be observed[4]. In rare cases polycythemia occurs. Normoblasts and megaloblasts occasionally are seen in the peripheral blood as are also myeloma cells. There is usually some anisocytosis and poikilocytosis. Autoagglutination and roulette formation are common, and the difficulty of preparing a blood smear or cross matching the blood may first suggest the possibility of multiple myeloma as the cause of the patient's anemia. In order to overcome this difficulty the blood grouping must be performed at a temperature above 8° C. This autoagglutination of the blood is due to the hyperglobulinemia which is responsible also for the anti complementary action seen in the Wassermann reaction of the blood in these cases. The relatively high hemoglobin content, high color index, compared to the reduction in cell count is often striking[4].

The white blood count is normal in about three-quarters of the cases; in the remainder a leukocytosis ranging up to 15,000 usually is found which is consistent with the degree of anemia. In about 7 per cent. of the cases leukopenia is observed. Myelocytes (1 to 10 per cent.), a mild eosinophilia (3 to 5 per cent.) and the occasionally abnormal mononuclear (Turck) cells and tumor (plasma) cells may be found[4].

Kidney

The kidney at autopsy, if affected during life, shows characteristic findings which have led to its being designated as the 'myeloma' kidney. In approximately three-quarters of all cases there is marked albuminuria, inability to concentrate the urine, a rise in the non protein nitrogen of the blood, secondary anemia and anemia indicative of renal insufficiency. The size of the kidney is not unusual, but it may be small and the surface pale. The cortex is narrowed and shows irregularity in the striations with roughening of the subcapsular area if arteriosclerosis is present also[9].

Histological study reveals changes in the tubules without significant glomerular involvement which led earlier workers to designate the condition as a form of nephrosis. The tubules are dilated and filled with huge hyaline casts which may appear laminated with peripheral striations[33]. These 'Eiweisssteine' or 'protein stones', as they have been designated[66], may be surrounded by a layer of amorphous protein material around which in turn are many neutrophilic leukocytes and multinucleated giant cells giving the picture of a foreign body reaction[4,43]. The medulla of the kidney may be replaced by connective tissue.

In addition to the blockage of the collecting tubules by deeply staining casts there may be an eosinophilic globular material in the cells of the convoluted tubules, interstitial edema and cloudy swelling of the convoluted portion of the tubules. The tubular epithelium is not sufficiently injured, however, to result in

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Hellwig[16] has reviewed and analyzed 127 cases of extra medullary plasmocy

toma which appeared in the literature from 1905 to 1942. About half, 67, of these cases originated in the air passages, 47 in the conjunctiva, 4 in the lymph nodes and 13 in other organs (pleura, mediastinum, spermatic cord, thyroid, ovary, testis, intestines, kidney, skin and mouth).

Of the extra medullary plasma cell tumors which appear in the upper respiratory tract, half are non invasive solitary tumors, which appear in patients 40 to 80 years of age and are limited almost entirely to the male. They occur in the nasal cavity (turbinates, septum or lateral wall), nasopharynx, larynx, tonsils, fauces and floor of the mouth[75, 87, 93]. Histologically these tumors consist of the characteristic plasma cell, but an occasional tumor shows atypical cells resembling lymphoblasts. Symptoms arise from mechanical obstruction of the air passages. Following surgical removal usually there is no recurrence, but in an occasional case recurrence occurs and the disease ends with the generalized characteristic form of multiple myeloma. Thus in the case described by Jackson and his coworkers[60] the original site of the tumor, a typical plasmocytoma, was in the tonsil. This was removed but recurred. Eight years later the typical bone changes of multiple myeloma were apparent in the x ray. Blumenfeld[18] has collected 21 such cases from the literature in which extra-osseous lesions are the first manifestation, with the bone marrow only involved late in the disorder. Although the appearance of the tumors in the bones has been attributed to metastatic spread, it is more plausible to assume that these lesions represent only a late manifestation of a generalized involvement of the hematopoietic system.

In about 12 per cent of the cases the plasma cell tumors of the nasopharynx are multiple, but these, like the solitary tumors, manifest a low grade of malignancy. As many as 7 separate tumors have been described in a patient. These may appear also in the trachea and bronchi. The remaining half of the plasma cell tumors of the nasopharynx show local destructive properties. These histologically display a more atypical cell structure with a greater variation in size and form of the cells and nuclei and more mitotic figures[60]. In these patients there is pain due to invasion of nerves and hemorrhage with foul discharge. Radical operation and intensive irradiation or radium therapy is necessary to arrest the growth of these tumors.

Plasma cell tumors of the air passages in which there is enlargement of the regional lymph nodes are to be considered as malignant tumors with metastases. In other cases the metastases occur to the bones.

The conjunctiva is the site of plasma cell tumors which have been designated as plasmoma. These usually appear on the lids and have been considered as reactions to inflammation. The conjunctival plasma cell tumors are benign and recur only rarely after excision.

Extra medullary plasma cell tumors originating in the lymph nodes are rare, only 4 being recorded in the literature. Likewise only a few cases have been re-

ported to have originated in the thorax thyroid lacrimal gland ovary testis intestine kidney and skin In the case reported by Ulrich[1 4] a testicular tumor without other extra osseous involvement occurred

In general the extra-osseous myeloma may result from 1) direct extension of an intra osseous tumor to adjacent tissues 2) by metastasis 3) independently as an autochthonous growth which appears simultaneously with the intra o seous lesions and 4) as a primary extra medullary tumor with or without secondary in vasion of the bone marrow

Although extra skeletal lesions in multiple myeloma may result also from direct extension of the tumors through the destroyed bone they appear at these sites usually autochthonously rather than by metastasis[1 0] Thus in case of mul tiple myeloma involving the bones one may observe the intra sinusoidal prolifera tion of plasma cells from the lining of the sinuses and the presence of plasma cells throughout the red pulp of the spleen In the lymph nodes also the plasma cells proliferate in the interfollicular tissue[70]

The commonest sites of extra skeletal involvement are the visceral organs particularly the lymph nodes liver and spleen Nodular infiltrations have how ever been observed also in the kidneys lungs heart skin subcutaneous tis sue tonsils thyroid testis ovary gastrointestinal tract uterus adrenal and dura[2 8 53 54 58 59 99 109] These may be evident only on microscopic examination The appearance of the typical plasma cells in these visceral sites has an impor tant bearing on the probable nature of the disorder for it indicates that it is of systemic rather than of local origin and that the tumor cells may arise any where within the body where reticuloendothelial tissue is present

The involvement of the spleen which has been recorded in 6 cases gives a picture resembling that of sarcoma of myelogenous origin and these sometimes have been designated erroneously as primary myelogenous sarcoma of the skull bone

Other Disturbances

Amyloidosis is associated with multiple myeloma in about 7 per cent of all cases However it is also occasionally accompanied by tumor like deposits of amyloid in the striated muscles kidneys intestines and in and about the joints[39 71 107 1 1] This amyloid usually is not abundant in the usual sites in the *organs where it is found in other forms of amyloidosis and has atypical staining* reactions Its presence has been accompanied by Bence Jones proteinuria in the cases in which it has been found The involvement of the muscles and joints by the amyloid gives a clinical picture which simulates rheumatoid arthritis Magnus Levy[76] has suggested that the amyloid is derived from Bence Jones protein but this is questionable

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Pathological fracture may be the first presenting symptom Relatively slight injury may result in fracture of a rib In other cases fracture of the clavicle femur or of the spinal vertebrae resulting from slight cause as lifting a weight may bring the patient to the physician s attention Multiple fractures are common The healing of these fractures is slow but may occur as shown in Figure 3

Anemia although rarely of a sufficient degree to induce symptoms of complaint may be the first objective finding and lead to a discovery of myeloma as the primary disorder

The appearance of multiple palpable tumors may be the initial symptom These are present in about a third of all cases and in most cases involve the ribs sternum clavicles and spine In about half the cases there is involvement also of the skull the shoulder and pelvic girdle or the trunk The tumors are variable in size very painful to touch and are often pulsatile They are elastic and show crepitation They may vary in size due to the tendency of the vascular tumor tissue to undergo spontaneous hemorrhage which subsequently is resorbed The skull is tender to pressure as are also the swollen costo-chondral junctions when these structures are involved

The patient with multiple myeloma in its advanced stages assumes a characteristic posture in which the feet are set apart the abdomen protrudes and the ribs bulge and rest on the pelvic brim[43] Walking causes pain and easy fatiguability and each step is made cautiously and with deliberation When the bones of the head are involved there may be difficulty in mastication and the chin may droop resting on the chest

Chronic bronchitis and emphysema probably secondary to the bony changes in the chest and the cachexia occur in about half the patients These are however late manifestations There may be dyspnea tachypnea paroxysmal attacks suggestive of asthma and chronic cough with the production of a mucopurulent sputum Pain in the chest and painful respiration are observed commonly Terminally pneumonia is frequent

Disturbances of the gastrointestinal tract are presenting symptoms in about 20 per cent of cases[13] In some patients abdominal pain due probably to pressure on the nerve roots may suggest an acute abdominal condition[114] Hemorrhage from the gastrointestinal tract sometimes is observed Whether this results from decreased coagulability of the blood which presumably is responsible for the epistaxis observed in some cases or from involvement of the gastric mucosa has not been established Late in the disease when cord lesions are present there may be diarrhea nausea vomiting colic and enteriti

Involvement of the spine which occurs in about half of the cases results in numerous neurological disturbances Fracture or telescoping of the vertebrae may give compression of the lower thoracic or lumbar cord with paraplegia Usually there is gradual onset of weakness and sensory changes in the lower extremi

The mobilization of the calcium from the bones and the elevated blood calcium level observed in multiple myeloma sometimes leads to calcium deposition in the kidneys lungs and other tissues[5] Secondary hyperplasia of the parathyroid glands may occur in response to the same cause In most cases of multiple myeloma however no hyperplasia of the parathyroids is evident

SYMPTOMATOLOGY

As is to be expected in a disorder with such varied pathological manifestations the symptoms manifested by the patient with multiple myeloma are protean In its early stages before striking lesions in the bones are recognizable there may be complete absence of symptoms or complaint, and the condition may be discovered only accidentally For example in a patient recently observed by the author the difficulty of cross matching the patient s blood due to autoagglutination of the corpuscles and the discovery of hyperglobulinemia led to the performance of a sternal biopsy which revealed the typical findings of a plasma cell myeloma There was no recognizable evidence of disease of the bones at this time nor any symptoms or complaint attributable to multiple myeloma

Pain may be considered as the outstanding symptom of multiple myeloma but usually it is vague and indefinite in the earlier stages of the disease Pain is absent in less than 5 per cent of the cases but it may not appear till injury of a bone occurs[43] Pain is absent in cases of extra osseous myeloma The pain may suggest rheumatism be wandering and intermittent and generally is confined to the back Since the spine and ribs are the bones most commonly affected in the early stages of the disease, backache pain in the chest and painful respiration are often the first symptoms of complaint In two-thirds of the patients the pain is in the lumbar or sacral regions in others over the ribs or sternum and in a few in the arms legs shoulders or other bones Girdle sensations and pain radiating down the legs are common and suggest a neuritic origin[96] The pain is aggravated by motion or pressure and is subject to periods of remission and exacerbation Sudden movement exertion or strain accentuates the pain and may result in severe pain lasting for several days followed by relief Severe backache with a tendency of the pain to radiate down the legs is a common symptom In the final stages of the disease the pain is agonizing with complicating nerve root pains paresthesias and neuralgias

The frequent localization of multiple myeloma in the spine results in backache and other neuritic pains as common early symptoms due to collapse of the vertebrae which causes compression of the cord radicular pains and other neurological symptoms The polyneuritis so often seen in multiple myeloma has been attributed to a sclerosing interstitial perineuritis due to the toxic action of products formed by the tumors but this seems unlikely



Fig 30 The skull in multiple myeloma An x ray of the skull of a 6 ear-old man with multiple myeloma showing the multiple small punched-out areas of decreased density characteristic of th s disorder

as in syphilis or thickened as in Paget s diseas of bone or in sarcoma In its early stages the long bones may show expanded cystic changes and later large areas of rarefaction Although some formation of new bone occurs this is only evident in the x ray Its absence helps to differentiate the condition from metastatic car cinoma in which sclerosis is common

The tumors in multiple myeloma tend to expand the cortex of the bone with out penetrating it in contrast to the metastases of hypernephroma which usually cause no cortical expansion

Other Laboratory Findings

In addition to the x ray findings certain other laboratory procedures allow one to suspect the presence of multiple myeloma or to establish the diagnosis The tendency towards autohemagglutination has been referred to already in an earlier section

ties which leads to stumbling Interruption of nerve impulses leads to difficulties in urination and a loss of libido Ultimately a flaccid paralysis of the legs with incontinence develops Involvement of other nerves may give paralyses of the hand or pharyngeal muscles neuralgia particularly of the intercostal nerves and radiculitis which may manifest itself as herpes zoster Blindness may result from thrombosis of the central retinal artery Other neurological signs are exaggerated reflexes a positive Babinski sign and ankle and patellar clonus

The changes in the bones give rise to a variety of deformities in the spine, sternum ribs shoulder and pelvis, but not in the long bones as in other generalized bone disorders In the spine there is an obliteration of the lumbar curve, thoracic kyphosis and telescoping of the vertebrae There may be a depression of the angle of Louis and deformity of the gladiolus Nodules along the costo-chondral junctions give rise to the "parasternal rosary"[43]

Symptoms due to a localized myeloma of the bone usually are limited to pain enlargement at the site of the tumor or pathological fracture In the case of plasmocytoma of extra osseous tissues the *first symptom* of complaint usually is the presence of a local tumor which when present in the naso pharynx, may result in obstruction of the respiratory tract

X RAY FINDINGS

The appearance of the bones in the x ray are characteristic and usually allow the recognition of the disorder in about 97 per cent of all cases In its early stages there may be no radiological evidence of the disorder except perhaps for a suggestion of osteoporosis In some cases the changes in the bones may be so minimal as to remain unrecognized even when the typical blood changes, anemia hyperglobulinemia hypercalcemia are present and the disease is diagnosable from the sternal puncture At times the roentgen appearance may show a diffuse type of infiltration with comparatively little destruction of bone[83]

The characteristic change in the x ray is bone destruction which appears as punched out rounded areas which show no tendency towards new bone formation (Figs 30 31 3) At times there is *diffuse decalcification or mottling* The ossified costochondral junctions are often the site of bone absorption The tumors on the ribs may appear to be projecting inwards[107]

Where pathological fractures occur there is a tendency for deformity rather than bending (Fig 32) Involvement of the spine may appear as rarefaction globular tumor formation, infraction collapse or disappearance of the intervertebral disc

The skull often gives a diagnostic appearance with multiple punched out areas (Fig 30) which may be confined to the frontal and upper parietal areas These are not as large as those seen in metastatic carcinoma, nor do they appear mottled



Fig 32 Shoulder girdle and humerus in multiple myeloma An x ray of a 46-year-old woman with multiple myeloma showing the multiple punched-out areas in the bones and a pathological fracture through the proximal third of the humerus There is slight lateral bowing at the site of fracture and callus formation about the edges

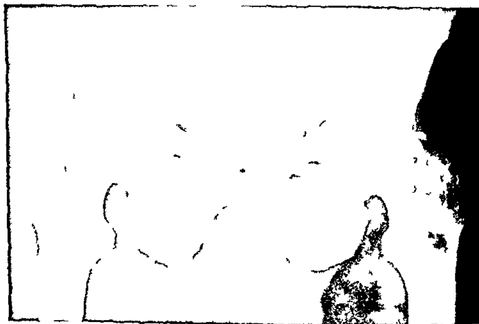


FIG 31 The pelvis in multiple myeloma The x ray appearance of the pelvis and heads of the femora in the same patient as in figure 30 showing the typical changes of multiple myeloma Note the coarse accentuation of the trabeculae of the bones the generalized decalcification and the destruction of the cortical bone by the expanding medullary tumors

Sternal Puncture

The sternal marrow is almost always affected in multiple myeloma even in cases in which no tumor of the sternum is evident For this reason examination of the smear obtained by sternal puncture often leads to diagnosis of the disease even in cases where it has not been suspected[9 78 10a 1a] Examination of the sternal marrow reveals the presence of the characteristic myeloma cells (Fig 29) which may comprise from 3 to 65 per cent of all the cells The marrow usually is cellular Since the infiltration of the marrow is often nodular rather than diffuse the characteristic cells may be missed, if the aspiration needle fails to penetrate an involved area

Bence Jones Protein

Bence Jones protein which is so characteristic a finding in multiple myeloma, occurs in about two thirds of all cases However the finding of this abnormal protein is not entirely pathognomonic for it may occur also in other bone and blood diseases which involve the red marrow[19]



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Bence Jones protein coagulates usually between 50 to 60° C, rarely as low as 43°, and redissolves at 90 to 100° Hence it may be detected by heating the urine in a water bath and noting the appearance of a coagulum at 50 to 60° which disappears as the temperature is raised to the boiling point [4]

In many cases of Bence Jones proteinuria the simultaneous presence of albumin in the urine renders the detection of the former by the simple means just outlined impossible In such a case it is necessary to add 0 5 c c of N sodium acetate and 0 5 c c of N acetic acid to 10 c c of the urine and heat the mixture slowly on a water bath to boiling when the albumin is precipitated The hot solution is filtered rapidly through a heated funnel, allowing the solution containing the Bence Jones protein to pass into the filtrate, where its presence is detected by the usual procedure An alternative method for removing the interfering protein consists in saturating the urine with sodium chloride and adding one tenth volume of 0 per cent sulfosalicylic acid heating to 100° C and filtering rapidly through a heated funnel Only the Bence Jones protein remains in the filtrate[116]

The view that the Bence Jones protein is responsible for the observed renal disturbance seen in multiple myeloma is supported by the fact that both occur together in about 60 per cent of all cases No Bence Jones proteinuria is found in about one third of the cases and some form of renal disturbance without Bence Jones proteinuria in about one quarter of the cases[43]

It is believed that the Bence Jones protein is formed by the myeloma cells for it tends to occur in cases in which these cells are large Since the cells vary in appearance it is not surprising that Bence Jones protein may appear only intermittently especially in the earlier stages of the disease Hence it should be looked for repeatedly

Bence Jones proteinuria usually is not associated with marked hyperproteinemia, however the two conditions may coexist

The Bence Jones protein when subjected to electrophoresis behaves like the β globulin of normal serum[17 3] A high molecular crystallizable protein has been observed also in the blood serum and within the plasma cells Whether or not this is identical with the Bence Jones protein is questionable

Blood Chemistry

The blood proteins may be altered markedly in multiple myeloma There is a tendency for an increase in the total protein the globulin being principally affected[13 14 6] The blood albumin on the other hand may be decreased

The change in the composition of the blood proteins is in most cases only moderate In about one third of all cases the plasma proteins are within the normal range Usually there is only an increase in the globulin content with a corresponding increase in total protein to 8 to 9 per cent The total protein how

ever may be as high as 12 to 14 per cent or twice the normal value and values over 20 per cent have been reported The blood albumin usually varies from 1 to 4 per cent the globulin from 9 to 11 per cent the A/G ratio from 0 15 to 1 0 The fibrinogen is increased also to 0 6 to 0 8 per cent as compared to the normal (0 2 to 0 3 per cent)[51] The protein osmotic pressure of the blood was not elevated in the one case in which it has been measured[101] The increase in the globulin and fibrinogen content of the blood is believed to be an immunological reaction since similar changes are observed following immunization with foreign proteins

The hyperglobulinemia of multiple myeloma may be due to an increase in any or all of the globulin fractions (pseudoglobulin I or II euglobulin) Only exceptionally however is it due to an increase in the pseudoglobulin II fraction In most cases however the euglobulin with or without the pseudoglobulin I fraction is increased The presence of hyperglobulinemia is responsible for the positive Takata Ara and its modified precipitation tests observed in multiple myeloma The Takata Ara reaction is positive in all cases of multiple myeloma in which the euglobulin content of the blood is increased The formol gel or aldehyde reaction is positive in all cases of hyperglobulinemia regardless of the fraction involved This reaction is carried out by adding two drops of 40 per cent formalin to 1 c c of blood serum After standing at room temperature for 3 hours the formation of a milky gel indicates a positive reaction This reaction is also positive in other disorders (e g kala azar) in which there is hyperglobulinemia[15]

The most common causes of hyperglobulinemia are chronic infections such as tuberculosis syphilis lymphogranuloma venereum Boeck s sarcoid subacute bacterial endocarditis kala azar and leprosy, in which there are also changes in the reticuloendothelial system with the accumulation of plasma cells In liver and kidney diseases hyperglobulinemia with low serum albumin is common but the total protein in these cases usually is low or only moderately elevated[64] The hyperglobulinemia observed in leukemia notably monocytic has been attributed also to the release of protein by the leucocytes

The sedimentation rate often is greatly elevated over 100 mm per hour This is a result of the tendency of the red blood cells to agglutinate[101]

The blood protein may be low in the late stages of the disease but at times remains at a high level despite the attendant cachexia

The blood serum calcium is elevated in about two-thirds of the cases to 12 to 18 mgm or more per 100 c c (normal 9 5 to 11 5)[51] Terminally the blood calcium may be reduced below normal The inorganic phosphorus remains within normal limits except in cases where impairment of renal function causes phosphorus retention The serum alkaline phosphatase also remains within normal limits or shows only an insignificant increase When renal insufficiency is marked there is the usual retention of the non protein nitrogenous constituents of the blood[3 4 98 1 2]

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the first onset of symptoms The longest duration of life of any proved case in the series of Geschickter and Copeland[13] was 5½ years but cases surviving 6 and 10 years respectively have been reported[13]

In the exceptional cases where the myeloma i limited to a single bone the patient may remain well for many years following local treatment The same is true where the site of primary involvement is in the lymphoid tissue Ultimately however these relatively benign local involvements may become generalized and give rise to the rapidly fatal typical multiple myeloma

Multiple myeloma like lymphoma manifests varying degrees of malignancy It is probable that many cases remain unrecognized for a long time as localized relatively benign lesions

Treatment

The treatment of multiple myeloma as of other inoperable malignancies is purely palliative The patient should be at rest to prevent fractures and minimize pain

Orthopedic measures are indicated when necessary Deep x ray therapy is useful for the control of pain and for the acceleration of healing at points of fracture Blood transfusions are of temporary aid in counteracting anemia

Recently two new drugs nitrogen mustard and stilbamidine have been used in the treatment of multiple myeloma The preliminary results obtained by the use of these drugs warrant their further trial Nitrogen mustard in the form of methyl bis (β-chloroethyl) amine hydrochloride has been found to exert biological effects similar to those induced by x ray irradiation In view of this action it has been used experimentally in the treatment of certain neoplastic disorders involving the lymphoid and erythropoietic tissues (Hodgkin s disease lymphosarcoma leukemia etc) Jacobson and associates[139] used the drug in two patients with plasma cell myeloma with some relief of pain but the remission was of short duration and the subsequent course of the disease was not affected The present writer has observed essentially similar results on 5 patients in all of whom there was marked remission of the pain with some symptomatic improvement in 3 of the patients Snapper[140] has reported more effective results by the intravenous injection of 150 milligrams of stilbamidine (4,4-diamidino-stilbene) daily for 15 or more days combined with a diet low in animal protein In 15 patients treated in this manner there was relief of pain with an apparent remission in the course of the disease in some cases The present author has used the combination of nitrogen mustard followed by stilbamidine in 5 patients but further studies are indicated before the value of these newer forms of therapy can be properly evaluated

In the rare instances of myeloma limited to a single bone excision is indicated Cases are on record in which recurrence had not occurred 4 years following the

Diagnosis

The cardinal diagnostic clinical signs of multiple myeloma, which may be present in part or in their entirety are[43] 1) multiple tumors of the skeleton in a person over 35 years of age 2) pathological fracture of a rib 3) Bence Jones proteinuria 4) lumbar backache and signs of early paraplegia 5) an unexplained anemia 6) chronic nephritis with azotemia and normal blood pressure 7) changes in the blood characterized by hyperproteinemia hypercalcemia autohemagglutination and a greatly elevated sedimentation rate The characteristic findings in the bones blood sternal marrow and urine in multiple myeloma render its recognition easy in most cases The disease is to be suspected in cases of musculoskeletal pain renal disturbances in which there is a high grade of albuminuria with a high serum protein in severe osteoporosis in cases of autoagglutination of the peripheral blood with rouleaux formation a high sedimentation rate and pathological fractures X ray examination often fails to differentiate between multiple myeloma and metastatic carcinoma or between a localized myeloma and other tumors of bone In such cases examination of the sternal marrow or biopsy will establish the diagnosis

In patients, in whom numerous plasma cells appear in the blood stream the condition may be mistaken for a plasma cell leukemia, particularly if there is no evident myelomatous change in the bones (See Leukemia Chapter XVII Vol II of Oxford Medicine) However, as already indicated, many consider plasma cell leukemia as only a leukemic form of myeloma

The high calcium of the blood and generalized decalcification seen in multiple myeloma have led occasionally to its being confused with hyperparathyroidism[5] In the latter condition however the inorganic phosphate of the blood is reduced (except in cases of renal insufficiency) and the alkaline phosphatase level is elevated[51] Only rarely does one observe the punched-out areas in the skull seen in myeloma A sternal puncture, in case of doubt will differentiate the two conditions

The rare monostotic form in which multiple myeloma affects a single bone, may be mistaken for a giant cell tumor Biopsy in these cases reveals the true nature of the disorder The involvement of the sternum may be mistaken also in the lateral view of the x ray for a mediastinal shadow The changes in the skull may be mimicked by the lesions of Schuller Christian disease

The extra osseous forms of myeloma such as plasmocytoma of the nasopharynx or plasmoma of the eyelids are readily diagnosed by biopsy of the tumor

Course and Duration

Multiple myeloma shows the steady progressive course with cachexia characteristic of malignant disease The average duration of life is about 2 years from

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amputation of a leg[103] 18 months following excision of a localized lesion in the skull[51] 6 years following irradiation of a solitary tumor of the humerus and 1 year following curettement of a similar tumor[11] Spontaneous regression has also been reported[1, 9] In the case of plasmocytoma and plasmoma of extra-osseous origin likewise local excision is indicated Recurrence, however, in these cases is not uncommon[7]

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Part XII

MISCELLANEOUS LESIONS OF THE BONES

Introduction

In the present section are included several relatively rare conditions of clinical interest which are not discussed in previous sections or included in Chapters XLIII XLIIIA and XLIIIB of Vol V of Oxford Med on Rare Diseases by F R Taylor In the latter will be found descriptions of osteosclerosis or marble bones arachnodactyly arthrogryposis multiplex congenita Morquio s disease hereditary arthrodysplasia with dystrophy of the nails hypertelorism Bruck s disease hereditary enlargement of the parietal foramina cleidocranial dysostosis craniofacial dysostosis acrocephalosyndactylism craniofacial amphiarthrosis acrocephaly dystrophia periostalis hyperlastica familiaris gargoylism acromicria leontiasis ossea hemiatrophy and hemihypertrophy

BASILAR INVAGINATION OF THE SKULL
(*Platybasia*)

Introduction

This congenital or acquired anomaly is of clinical interest because unlike most developmental defects it does not manifest itself until later life and presents a picture suggestive of organic neurological disease

Historical — Anthropologists and pathologists have long been acquainted with this condition but it has only received attention by clinicians in recent years Schuller in 1911 noted the roentgenographic features of the disease and Ebenius[4] in 1934 described 4 cases in which clinical symptoms resulted from the anomaly In 1939 Chamberlain[1] described 4 additional cases and brought the condition to the attention of American physicians Craig Walsh and Camp recently have reported 3 Ray [8] 4 and Stevens 1 case on whom operation was performed These authors have reviewed the earlier work and described in detail the symptomatology and treatment of the disorder

Definition —A craniovertebral anomaly, congenital or acquired, which may be accompanied by neurological symptoms due to compression of the brain stem as a result of invagination of the base of the skull

Synonyms —Platybasia basilar invagination or impression of the skull The term platybasia as used in anthropology denotes an abnormal obtuseness of the sphenoid angle included in lines from the foremost point of the foramen magnum to the center of the sella turcica and from the latter point to the root of the nose This condition gives rise to no symptoms The condition, which has been designated clinically as platybasia, is better designated as basilar invagination of the skull

Etiology

In the congenital forms of the disorder, which are observed most commonly, there is a developmental anomaly of the occipital bone and upper cervical vertebrae which results in compression of the underlying spinal cord and brain and is responsible for the observed neurological symptoms Occasionally, however, the condition may be acquired due to some primary bone disease as in the two cases reported by Ray[18] which were secondary to Paget's disease and fragilitas ossium respectively A condition comparable in its effects to that observed in platybasia has been observed following fracture with rupture of the transverse ligament of the axis and displacement of the odontoid process and compression of the cervical cord This has been designated as pseudoplatybasia[4]

The symptoms in platybasia arise from compression of the brain stem due to narrowing of the posterior fossa with flattening of the cerebellar hemispheres occlusion of the cisterna magna, herniation of the cerebellar tonsils into the spinal canal and constriction by the projection of the occiput into the foramen magnum

Pathology

The craniovertebral deformity responsible for the development of the disorder includes a variety of anomalies of the occipital bone atlas and axis There results an upward displacement of the posterior cranial fossa around the foramen magnum The elevated portion of the occiput is thinned, and the condyloid process remains rudimentary[7] Frequently there are also variations in the upper cervical vertebrae, the first being rudimentary in type with its posterior arch fused to the lower surface of the occipital bone The spinous processes of the second and third cervical vertebrae may be fused also

There is a tendency for adhesions to form about the herniated portion of the brain stem and cerebellum It is these adhesions which are probably responsible for many of the symptoms of the disease[9] Hydrocephalus may result from blockage of the medullary canal[18]

Symptomatology

The clinical picture is exceedingly variable The patient often presents a characteristic appearance with the head projected forward a short neck and low hair line The neurological symptoms may simulate neoplasm of the posterior fossa or upper cervical canal hydrocephalus multiple sclerosis or spinocerebellar disease Some cases give a picture of syringomyelia[8] with dissociation of sensory loss as a result of compression of the ventrolateral tracts The symptoms usually develop insidiously during adolescence or early adulthood and progress thereafter

As in other congenital anomalies platybasia may be accompanied by other developmental abnormalities Anomalies of the occipital bone atlas and axis may be present such as the Klippel Feil deformity in which two or more cervical vertebrae are fused[15] or the Arnold Chiari deformity in which the pons and medulla oblongata are lengthened with herniation of the cerebellum into the spinal canal Spina bifida occulta due to failure of fusion of one or more vertebrae and cavitation of the cord syringomyelia and syringobulbia may complicate the condition also [5]

Involvement of the cerebellum midline cerebellar strictures and cranial nerves give rise to ataxia nystagmus difficulty in swallowing weakness and other motor, sensory and proprioceptive disturbances suggesting involvement of the upper cervical cord and brain stem

X Ray Appearance

The roentgenogram is pathognomonic the demonstration of invagination of the basioccipital region of the skull establishing the diagnosis [1] In many cases however there may be roentgenographic evidence of platybasia without any symptoms

The x ray in congenital forms of the disorder reveals in the lateral view the rudimentary development of the occipito atlanto-axial region dislocation of the atlas and axis upward and forward and invagination of the posterior rim of the foramen magnum In the sagittal views taken in the anteroposterior direction asymmetry of the posterior cranial fossa and of the foramen magnum and upward dislocation of the atlas and axis are evident[18, 1]

Differential Diagnosis

Platybasia should be kept in mind as a possible cause of neurological symptoms of a bizarre character suggestive of tumors of the brain stem cerebellum, posterior fossa or upper cervical canal hydrocephalus syringomyelia syringo

bulbar multiple sclerosis or spinocerebellar disease The diagnosis is established by the x ray findings described above

Treatment

Operation is indicated in all cases of platybasia manifesting symptoms, for improvement of existing symptoms and prevention of progression of the disorder follow suboccipital decompression The dura must be opened to obtain satisfactory results but intradural manipulations should be avoided[18] The foramen magnum may be enlarged by removal of its posterior arch and the spinous processes and laminae of the upper cervical vertebrae Adhesions between the brain stem and cerebellum should be freed[7] The operation is not hazardous and in many cases leads to gratifying results[9]

TIETZE'S DISEASE

(*Non Suppurative Non Specific Swellings of Rib Cartilage*)

Historical — In 1921 Tietze [3] described 4 patients manifesting swellings of the costal cartilages associated with little or no constitutional disturbance Hartung[10] in 1923 described a similar case and referred to another reported by Froehlich in 1921 before the Medical Society of Breslau, at which meeting Kuettner in the discussion mentioned several similar cases[6] In 1937 Satani and Fujii[19] reported 9 additional cases and recently Gill Jones and Pollak[6] reported 5 cases

Definition — A non suppurative non specific swelling of the rib cartilage of unknown etiology

Etiology

Satani[19] attributed the disorder to malnutrition which may also have been a factor in Tietze s patients [3] but there was no evidence of undernourishment in Gill Jones and Pollak s patients who were young well fed soldiers[6] The pathological findings are not such as would suggest an infectious origin The condition in the patients of Gill, Jones and Pollak[6] was associated with respiratory infection

Sex and Age — Both males and females are affected The disorder has been noted only in adults varying in age from 21 to 50 years

Pathology

The lesions are firm and confined to the rib cartilages which are expanded locally The skin over the affected areas remains normal and freely movable

Biopsy[1] reveals fibrosis ossification and atrophy with no granulation tissue or inflammation Nodules of fibroblasts and giant cells[10] may be encountered The chondral tissue may show an irregular arrangement suggestive of a neoplasm, and the perichondrium muscles fascia and ligaments may be thickened[6]

Symptomatology and Course

The condition is insidious in onset with a painful and prolonged course characterized by fluctuations in the size of the swellings No evidence or signs of suppuration appear The tenderness may disappear or recur One or more ribs may be affected

The swellings are diffuse and spindle shaped encroaching on and at times filling the intercostal spaces Constitutional symptoms are not present

X Ray Findings

Examination by x ray may reveal no abnormality or evidence of calcification[19] There may be atrophy of the rib cartilage and shortening of the rib

Treatment

The condition is self limited and requires no treatment Biopsy may be necessary to establish the diagnosis

OTHER RARE DISEASES OF BONE

Among other lesions of the bones of clinical interest which have received attention in the recent literature may be mentioned the following

Melorheostosis

This is a very rare condition described first by Leri and Joanny[14] in 1922 The name is derived from the Greek μελος limb ρεος flow and οστεον bone in allusion to the appearance of the affected bones which resemble the incrustations of the drippings on a wax candle ' coulee de bougie There is a marked thickening of the bones by irregular overgrowths projecting from the cortex with some encroachment and narrowing of the marrow cavity in advanced cases of the disease Multiple bones of one extremity usually are involved but the condition may be bilateral The x ray appearance described by Leri and Joanny[4] as the

"coulée de bougie" is pathognomonic and easily differentiated from the other conditions in which hyperostosis of the cortical bone occurs

In addition to the bones of the extremities cases have been reported in which the parietal mandibular vertebral and innominate bones and the ribs have been affected Microscopically one observes distortion of the normal osseous structure with an increase in density of the bone and diminution in the size and number of the Haversian canals The symptoms are not striking and are due to the increased weight of the affected limb or asymmetry due to the bony thickenings Nothing is known regarding the etiology of the condition nor is any treatment available[16]

Solitary or Eosinophilic Granuloma

In this condition which appears during late childhood or in the young adult there are solitary destructive tumors of the bones characterized microscopically by an eosinophilic infiltration of the reticuloendothelial tissue Over a score of cases have been reported since the original description of the disease in 1929[8] Since the histopathological appearance of the lesions resembles that of solitary xanthoma and of Hand Schuller Christian s disease, recent authorities believe these conditions as well as Letterer Siwe s disease to represent fundamentally the same condition[16] This view is strengthened by the finding of transition forms intermediate between the typical Hand Schuller Christian disease and the classical eosinophilic granuloma

Roentgenographically the eosinophilic granulomata resemble what is seen in other forms of the reticuloendothelioses The condition is characterized clinically by swellings of the bones usually single but occasionally multiple with at times low grade fever, leucocytosis and eosinophilia The diagnosis may be suspected from the x ray, but a biopsy is essential for establishing the diagnosis The tumors are benign and disappear following irradiation or excision [17]

Osteoid Osteoma

This condition formerly misclassified as an instance of sclerosing non suppurative osteomyelitis or cortical bone abscess was shown by Jaffe[11] to be a clinical entity The lesion consists of a small spherical nodule of vascular mesenchymal tissue filled with osteoblasts which deposit osteoid tissue that calcifies very slowly The small primary focus ultimately becomes calcified to an abnormal degree and surrounded by a mass of very dense cortical bone The lesions occur in the shafts of the cortices of the bones of the extremities and in the vertebrae of individuals more commonly males between the ages of 10 and 25

The principal symptom is persistent slight pain with some tenderness and swelling The lesion appears in the x ray as a round or oval translucent or opaque area 5 to 10 mm in diameter surrounded by an area of dense bone Treatment consists in excision which is followed by relief of pain with no recurrence The etiology is unknown[1 16]

Aseptic Necrosis and Caisson Disease of Bone

Victims of caisson disease may undergo extensive aseptic necrosis of numerous tubular bones of the extremities due presumably to the extravascular liberation of gas bubbles which impede the circulation However similar lesions may appear also in patients not exposed to high pressures hence the pathogenesis of the disorder is uncertain [13]

The condition resembles that seen in certain forms of osteochondroses Legg Perthes Osgood Schlatter s Koehler Freiberg s and Kienbock s diseases The symptoms and deformities depend upon the site area and degree of involvement of the bone If situated in the epiphyses bordering a joint collapse of the weight bearing portion of the bone a loosening of the articular cartilage and arthritis deformans may develop When involving the diaphyses encapsulated and calcified areas appear

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CHAPTER XVII

THE PHYSIOLOGY AND PATHOLOGY OF WORK

By CECIL K. DRINKER AND KATHERINE R. DRINKER

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THE NATURE OF THE PROBLEM

The physiologist and the psychologist divide work into two varieties, mental and physical, but in order to make such a separation approach completeness the best resources of the laboratory are necessary. It is

a safe statement that no sort of gainful work can present an isolated instance of either mental or muscular activity In all types of occupation there is a combination of the two with a predominance upon one or the other side As a consequence we may expect the results of work to register themselves through a variety of such combinations In the words of the final Report upon Industrial Health and Efficiency of Munition Workers published by the British Ministry of Munitions 1918 Fatigue may spring (a) from the maintained use of intelligence and observation with varying degrees of the muscular effort necessary in every kind of work or (b) from the maintenance of steady concentration upon one skilled task or (c) from distributed attention as when several machines are to be tended or other manipulations performed or (d) it may depend upon the continued use of special senses and sense organs in discrimination whether by touch or sight or (e) upon other parts of the body acting upon the nervous system"

Work involves expenditure of energy and if it is to be continuous demands a constant supply of energy yielding material and maintenance of conditions favorable to the use of this material There are thus two chief sets of processes operative in the work of human beings first the actual prosecution of the task involving breakdown of energy yielding material and certain possibilities of mechanical wear and tear and second restitution of the parts involved The physician more readily than the physiologist or the experimental psychologist accepts the possibility of protracted and far reaching effects from types of exertion apparently very simple It is his duty to detect breakdown and to watch restoration He realizes that while man may in time of necessity draw upon an extraordinary reserve of power for continued success in these days of overstrain he depends not so much upon his capacity for execution of work as upon his capacity to restore evenly all that work may do to him It is the waning of restorative power which in the end distinguishes the old from the young the well from the ill The literature upon work and fatigue is replete with descriptions of breakdown but even in the cases of the simplest laboratory experiments such as those upon the nerve muscle preparation of the frog there is little information upon recovery

The importance of this lack of knowledge is very apparent when one views the most recent work upon industrial fatigue Each factory employee must be considered not only in terms of his output per day but in terms of his output per year and continued output demands complete power of repair When any accurate estimate is to be made as to the harmful effects of work it should be attended by a careful medical examination of the subjects involved and this examination must not only bring out the fact that the individual to be studied has let us say a hernia which will prevent him

from successful prosecution of the work in hand but should also determine the probabilities for protracted work in each individual case. A heart lesion, arteriosclerosis, history of breakdown in previous jobs, all these and many other facts present evidence that this man may fail to repair as perfectly as he should and may consequently register the harmful effects of work.

To study fatigue therefore we must correlate information upon the fundamental physiology of muscle, nerve and central nervous organs with information upon other bodily processes which may influence its development. No bodily reaction is isolated; not one is affected by a single set of conditions or put in motion through a single cause; all are played upon by a multitude of influences, and although our discussion of fatigue may display limitations in treatment, this is not due to failure to realize the breadth of the problems presented by human work and fatigue.

The Modern Conception of Muscle and Nerve Physiology

The Organization of the Neuromuscular Apparatus

In order to appreciate the functioning of nerve and muscle it is necessary to recall certain facts in regard to their structure and development. Waldeyer in 1891 appreciated the unit character of the neurone, and subsequent work has not demonstrated the necessity for relinquishing his view. Three classes of neurones exist: (a) Afferent or sensory neurones extending from the surface of the animal to the central nervous organs and transmitting sensory impulses. (b) Efferent or motor neurones connecting the central nervous organs with the muscles, glands, etc. (c) Association neurones, elements lying largely within the central nervous organs and connecting one part with another.

A typical nervous reaction in man involves all three sets and is known as a reflex. The reflex begins with activity of a sense organ or receptor from which a sensory impulse passes into the cord, where it is taken up by an association neurone, the adjustor, which in turn passes it out through a third link to the muscle or gland, which is called the effector. The ordinary reflex thus involves in sequence the activity of a receptor, adjustor and effector, and these three elements are recognizable in every reflex arc.

If we inquire into the steps by which the mechanism of the reflex has been developed it will give us a more intelligent conception of the way in which it functions. In the earthworm we have an animal which has at its anterior end a small brain from which a ventral ganglionic chain extends posteriorly through the rest of its body. It possesses sensory

a safe statement that no sort of gainful work can present an isolated instance of either mental or muscular activity In all types of occupation there is a combination of the two with a predominance upon one or the other side As a consequence we may expect the results of work to register themselves through a variety of such combinations In the words of the final Report upon Industrial Health and Efficiency of Munition Workers published by the British Ministry of Munitions 1918 "Fatigue may spring (1) from the maintained use of intelligence and observation with varying degrees of the muscular effort necessary in every kind of work or (b) from the maintenance of steady concentration upon one skilled task or (c) from distributed attention as when several machines are to be tended or other manipulations performed or (d) it may depend upon the continued use of special senses and sense organs in discrimination whether by touch or sight or (e) upon other parts of the body acting upon the nervous system

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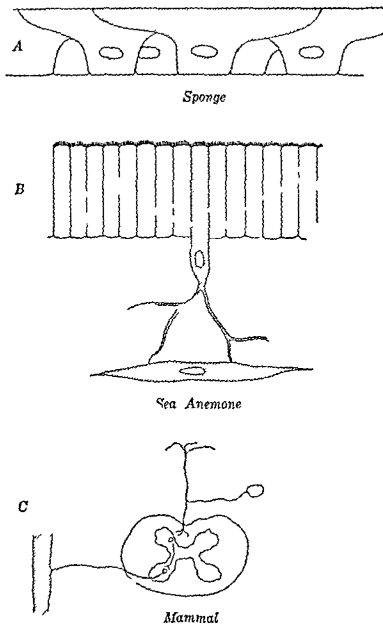


Fig. 1.—The development of the reflex arc

neurones which extend from the skin into this central nervous organ and motor neurones leading from the central organ to the muscles In the central organ adjustor neurones occur though they are not numerous The animal thus has all the fundamental equipment of man barring too few adjustors While it is possible that a certain degree of consciousness may attend the activities of these creatures they are in the main reflex machines and they owe this characteristic to the simplicity and fewness of their adjustor neurones A still lower type of animal such as the sea anemone possesses no adjustors whatsoever and again still further down the scale one of the sponges stylotella studied by Parker[1] is apparently without any specialized conducting mechanism being equipped with muscle cells which are capable of direct stimulation and thus act as independent effectors

It is thus clear that muscle appears before nerve and that as we pass up the scale to man the great difference which is noted is in the number of links the number of neurones through which the nervous impulse must pass before the muscle is thrown into activity The features of this development are shown diagrammatically in Fig 1

The Sites of Fatigue

(a) *Neurone Bodies*—For many years physiologists and pathologists have endeavored to obtain evidence that continued activity produces changes in nerve cells which can be recognized histologically If one takes under consideration such an activity as walking or swimming it is easy to understand that after the action is started it is carried on by reflex arcs which do not involve consciousness in the sense of requiring attention etc It is only when such an action is to be stopped or speeded up that higher centers are utilized Similarly one may consider that in reading the individual makes use of highly specialized paths in the cerebrum but there is no reason why the nervous activity involved should be other than that pictured for the simple motor phenomenon of walking In neither case can we determine how far if at all cerebral nerve cells originate impulses Modern conceptions of nervous activity lead us to believe that some sort of sensory inflow is necessary in order to initiate any nerve cell activity and on the basis of such a view the most complicated types of nerve function depend not upon some unusual property or origination in the nerve cells but rather upon the number and variety of contacts made by association neurones

It is of course known very definitely that the cell body is indispensable for the nutrition of the nerve fiber It is probable too that in many instances impulses must pass through the cell but Bethe[2] has shown

cell bodies but they must be considered invisible to our present powers of observation

(b) *Nerve Trunks* —Wedensky[6] in 1884 performed the experiment illustrated in Fig 3 In this case he first recorded a muscle twitch which signalled the passage of an impulse down the nerve He then blocked subsequent impulses by use of a galvanic current and after stimulating for six hours removed the block and at once obtained a contraction of the muscle quite comparable to the original one and indicating that rapidly repeated impulses passing down the nerve trunk for six hours produce no appreciable disturbance in conducting power Similar experiments have been carried out with a variety of preparations from a variety of animals and all agree in enforcing the conclusion that the nerve trunk is practically infatigable

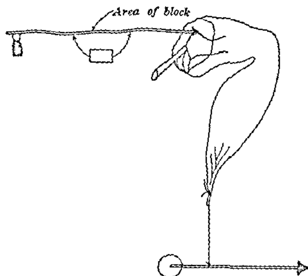


Fig 3 —Wedensky's experiment upon fatigue in the nerve trunk

Keith Lucas[7] and his collaborators have shown clearly that for 0 002 seconds following the passage of an impulse the nerve trunk absolutely refuses to conduct another impulse but that within 0 03 seconds following impulse passage the nerve conducts normally once more This demonstration of a refractory period together with Tashiro's[4] evidence that the conducting nerve produces carbon dioxide makes us think of the nerve impulse as a chemical process with a definite demand of time for restoration of original conditions before a second impulse may pass It is however certain that whatever the type of disturbance to which the

that the cell bodies are not necessary for reflex action in the crab and Steinach[3] has shown that the posterior root ganglia in the frog are not essential for conduction in ordinary sensory motor reflexes (See Fig 2) Tashiro[4] has studied the carbon dioxide output of conducting nerve fibers and of the large automatic ganglion in the heart of the king crab This ganglion is composed largely of nerve cell bodies which send out rhythmical impulses causing the heartbeat Curiously enough Tashiro finds from 2 3 to 4 7 x 10 ⁷ gm of CO given off by 10 mg of ganglion and a lower amount given off by a conducting nerve from the same animal It is thus evident that active nerve cells operate in an extraordinarily economical manner The oxygen consumption of the brain has been measured but not satisfactorily It is apparently not great

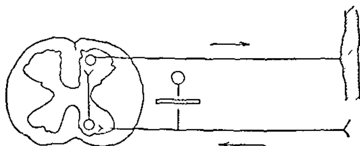


FIG 2 —Conduction in the reflex arc under the conditions of Steinach s experiment

From such unsatisfactory evidence it is easy to conclude that physiologists do not know what is taking place in nerve cells during any form of activity which may be under observation and it is disappointing to find that incessant activity leaves no reliable histological evidence indicative of nerve cell exhaustion Different workers upon the neuropathology of fatigue have reported alterations in the size of the cell body and nucleus and in the amount and distribution of chromatic material Kocher[5] produced exhaustion in dogs cats pigeons sparrows frogs and rats Every experiment was carefully controlled by a resting animal of the same species of the same approximate age and size and the material from both given identical treatment except for the activity The nerve cells studied were from the cruciate gyrus from the cerebellum from the anterior horn of the spinal cord and from the dorsal ganglia There was no deviation from the normal in even the most advanced fatigue

There is therefore no valid evidence that the neurone body is an important site of fatigue Future experimentation may provide methods by which certain elements in the fatigue process may be localized in the

In this instance there is a point of discontinuity at the junction of the upper and lower motor neurones The nerve impulse must at this point pass from one nerve cell to another Sherrington[8] has called such points of junction *synapses* and has succeeded in proving their extreme importance in the activity of the nervous system Clearly several synapses must be passed in any reflex involving the spinal cord and it was through the study of a reflex in the dog that Sherrington was enabled to establish the importance of the synapse in nervous fatigue

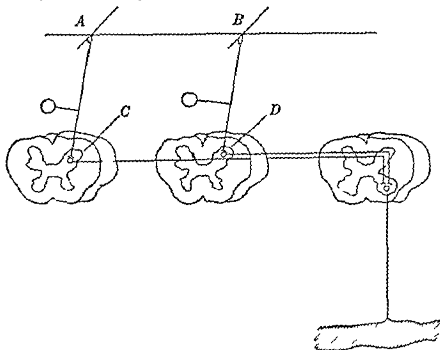


FIG 5 —Diagrammatic representation of Sherrington s experiment to illustrate location of fatigue in the synapse

Sherrington s experiment was carried out as follows If one irritates the skin of a dog s back anywhere throughout a large saddle shaped area, the stimulation is promptly followed by rhythmical scratching movements of the hind leg on the side irritated If the stimulation is continued the scratching will gradually grow less and less and eventually will stop Fatigue has occurred Sherrington first showed histologically that the path involved in this reflex has three links (1) A receptive neurone from the skin to the spinal gray matter (A and B Fig 5) (2) A long descending association neurone extending from the thoracic region to the leg segment

nerve impulse belongs there is in it such great perfection of adjustment and such great economy of operation that within the limits of possible activity no fatigue can occur

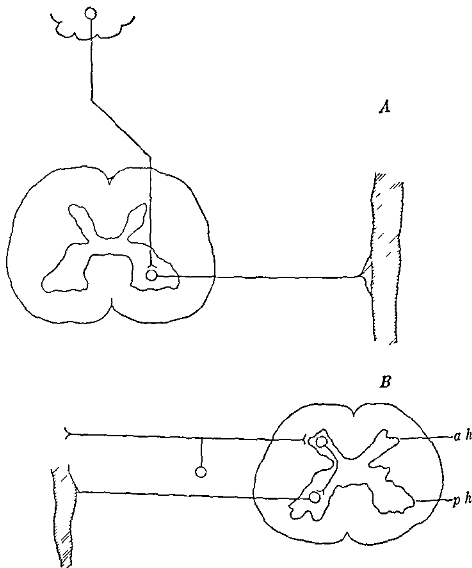


FIG 4 —(A) Conduction of motor impulse from cerebral cortex to muscle (B) Conduction in a simple sensory motor arc

(c) *Synapses* —The fact that the mammalian nervous system is a series of links is of the greatest importance in the consideration of fatigue Fig 4A indicates the simplest possible path which a nerve impulse may traverse in passing from the motor cortex to a muscle such as the biceps

we throw into activity more and more nerve cells endeavoring by utilization of other paths to compensate for those which have become impassable

In regard to the second of our contentions namely that at the moment when further lifting has become impossible we may experience some sudden influence which permits it to continue much can be said If one makes use of familiar physiological terminology what has happened is that as we continue lifting continue using certain nervous paths containing synapses the threshold for impulse passage of these synapses has steadily risen until no impulse can overcome it Is there any way short of rest by which this threshold can be lowered? We know that strychnin possesses as one of its most conspicuous properties the power to break down synaptic resistance and caffein to a less degree has the same effect Both of these drugs are however too indiscriminate in their action to be of significant benefit in fatigue

While it is clearly far from the final truth our present knowledge concerning the uncovering of unsuspected muscular power is entirely in terms of nerve endings and muscle and does not concern the brain and spinal cord There is good evidence that a sudden brace in the individual near exhaustion reflects direct changes in muscle cell and in the junctional area between the motor end plate and the muscle cell It is apparently essential that there be a concomitant lowering of synaptic thresholds in the cord so that impulses may pass readily but as yet direct evidence is lacking upon this point

(d) *Motor End plates*—When the nerve impulse is compelled to pass from nerve fiber to muscle cell there is again a junctional area which operates as does the synapse This means that if we stimulate a nerve repeatedly and record contractions of the muscle which it governs we shall eventually reach a condition in which the muscle will not respond to nerve stimulation but will respond when stimulated directly Many facts agree in localizing this failure in the myoneural junction and it thus becomes apparent that between the brain which may desire to drive a muscle to exhaustion and the muscle itself there is interposed a second chance for failure There is first the possibility that impulses may fail through increased synaptic resistance in the paths within the central nervous system and there is a second peripheral safeguard in the myoneural junction There is good evidence that this second type of resistance can be broken down Cannon[9] and his collaborators have shown that under certain circumstances there is secretion of adrenin into the blood stream and that this substance is peculiarly adapted to bring about reactions favorable to the stressed individual Among the effects of adrenin which these workers have described there is one which has direct bearing upon fatigue If a nerve muscle preparation diagrammatically comparable to that shown in Fig 3 is

of the cord (C and D, Fig 5) (3) A motor neurone from the anterior horn to the flexor muscles of the leg Of these three links the third is most important Upon a small group of motor neurones supplying the flexor muscles all impulses which eventually cause contraction of these muscles must play Such neurones represent a final common path to the flexor muscles

With these facts established Sherrington stimulated at a skin area A Fig 5 and continued this stimulation until scratching ceased He then transferred his stimulus to B another point upon the saddle and the scratch reflex was at once reassumed The same flexor muscles were involved hence there could be no question that fatigue in the first instance was muscular The final motor path was also common to both reactions and it was therefore not at fault Previous experience has taught us that the conducting nerve fibers involved are not fatiguable within the space of any such reaction as this and through somewhat complicated evidence we know that the receptor substance at A is not fatiguable There is therefore but one point where fatigue can be located and it is in the synapse between A and the common motor neurone It is important to keep in mind that fatigue in this reflex expresses itself not in muscular exhaustion but in a failure of the conducting mechanism No matter how advantageous it may be for the dog to scratch his flexor muscles fail to receive impulses which induce contraction and this failure is brought about in synapses within the spinal cord

There is no doubt that in a willed motor act such as repeated lifting of the hand and arm to a right angle with the body fatigue eventually expresses itself not because the muscles involved are exhausted but because the impulses passing from the motor cortex to the muscles meet synapses which as a result of repeated passage of impulses have eventually become so refractory toward conduction that passage cannot be effected Only two alternatives are then possible in order to reassume lifting These are (1) to increase the strength of the impulse so that it may break down the heightened synaptic resistance or (2) to experience some sudden general influence which lowers synaptic resistance thus permitting normal impulses to pass through and reach the muscles It is safe to say that the first of these never occurs The nerve impulse however started has but one value It is all or none No matter how great the willful effort larger impulses in single nerve fibers cannot be manufactured If we perform some rhythmical act such as lifting a weight with one hand we note that as the process goes on more and more muscles are becoming involved in it An action at first neat and expeditious involving the biceps alone gradually demands the activity of muscles in the shoulder and trunk This experience demonstrates the fact that as fatigue develops

fatigue curve with a single muscle cell one gets repeated contractions and then sudden total cessation of activity When this latter condition has been reached increase in the strength of the stimulus may again bring about contraction but if it does contraction will be of the value obtained previously Pratt thus demonstrated that what varies most in the single muscle cell is its threshold Under repeated stimulation the threshold rises until finally it is so great that no stimulus will break through

The bearing of these observations is obvious We must think as Lucas indicated several years ago of each muscle not as an entity in itself but as a musculature It is a group of many thousand units which are set in operation by stimuli of constant value If we lift a weight of five pounds we may use let us say a tenth of the muscle cells in the biceps As we continue the process lifting the weight rhythmically time after time we eventually experience such an increase in threshold on the part of the set of muscle cells originally employed that they drop out of activity and if the process is to be continued another group must become active In this way any contracting muscle must be considered to be a complex of resting and active cells Graded muscular activity is thus not a question of power upon the part of cells to contract gently at one moment and vigorously the next it is a matter of the number of cells activated The bearing of this conception of muscle physiology upon fatigue is found in the matter of threshold variation Clearly the individual muscle cell in the gradual loss of irritability which accompanies fatigue possesses a property best ordered to protect it against fatigue In no way could complete rest be assured more readily As has been said adrenin acting either upon the myoneural junction or upon the muscle cell has the property of rendering stimuli effective which in the fatigued state of the tissues have been ineffective

(f) *Summary*—There is no reliable evidence that fatigue is located in neurone bodies or in nerve trunks In the synapses in the motor end plates and finally in the muscle cells themselves we have evidence that fatigue expresses itself in the first two by failure to permit impulses to pass and in the last by failure to recognize impulses which may reach them These are to be regarded as provisions essentially protective for muscle the actively metabolizing member of the group of tissues involved

The Working Muscle and the Products of Fatigue

In addition to the increase in threshold for stimulation muscle undergoes certain other changes as a result of continued work Most conspicuous of these is the production of acid in readily appreciable amounts The researches of Fletcher and Hopkins[11] indicate that lactic acid is not only

used the muscle however being left within the body of the animal and circulated normally it is found that the strength of electrical stimulus necessary just to cause muscular contraction remains remarkably constant if the muscle is left quiescent This is true whether stimulation is applied through the nerve or by means of platinum needles thrust into the substance of the muscle If now the muscle is severely fatigued it is found that its threshold for stimulation rises that more current is required to produce contraction than was needed in the resting state This is true both of muscle substance stimulation and of stimulation through the nerve trunk It is clear that again in these rising thresholds we have a mechanism in the myoneural junctions and in the muscle cells themselves which is protective against fatigue and it is of importance to realize that adrenin will restore the irritability which has been lost as a result of fatigue

It is not proper to think that adrenin betters the condition of the muscle It simply renders the muscle incapable of failing to receive all the stimulation possible Such a provision is manifestly favorable for a spurt but not necessarily favorable for the muscular future of the individual It has not been shown experimentally whether muscles experiencing repeated return of irritability through adrenin injections may not eventually be driven to a state of fatigue from which recovery is exceptionally difficult William James has popularized the conception of the unexplored and unexploited energies which we all possess and there is no doubt that the apparently exhausted individual may suddenly display an accession of power which is most astonishing Frequently, in individuals under great stress we may see somewhat protracted displays of vigor which make us feel that the human being in normal times operates far below his real capacity It is clear however that such a conception may be quite untrue An emergency results in reactions which permit the individual to use his muscles past the temperate safeguards which are normally imposed It is of course highly advantageous to be able to transgress in this way in times of temporary need but one must remember that the organism has been permitted to commit excess with the powers it possesses not that it has been suddenly endowed with any real accession of power

(e) *Muscle Cells*—Recent investigations by Pratt[10] upon the fundamental properties of muscle cells have provided us with a far better conception of the way in which a large muscle such as the biceps really works By means of very ingenious apparatus Pratt succeeded in recording the contractions of single muscle cells He found that if he stimulated a single cell repeatedly its height of contraction did not fall off gradually but that the muscle cell like the nerve operates upon an all or none' basis that is when stimulated it contracts to the maximum possible at the moment or else it does not contract at all One cannot write the conventional

Bodily work with its accompaniments of heightened blood pressure and increased heart rate means invariably more blood per minute through the active muscles That the blood stream also supplies combustible material in the form of dextrose is probable but how far the immediate nutrition of working muscle is important for fatigue prevention is not known The fact that easily assimilable carbohydrate food is a most efficacious agent in carrying men through exhausting work has been frequently demonstrated but the rapidity with which such material is actually used has not yet been estimated accurately In the same way very small amounts of alcohol which will be burned at once may prove to be sources of muscular energy of some value but in this case the reverse result will appear if the dosage is great enough to produce any nervous effects

Muscle Tone

There is no feature of healthy muscle more characteristic than the state of slight constant tension in which it exists We speak of this tension as tone and recognize that in so far as voluntary muscles are concerned it is dependent upon the integrity of a reflex arc with receptors in the muscle observed and not in the skin nor in surrounding muscles Thus any section of nerve filaments leading from muscle cells to spinal cord (sensory elements) or any section of nerve filaments leading from the cord to muscle cells (motor elements) will result in loss of tone in the cells under observation

While the simple arc so described is fundamentally responsible for tone portions of the central nervous system may also influence it Thus some of the impulses flowing in from muscle may ascend the cord to other reflex centers vestibular nucleus cerebellum red nucleus or corpus striatum and descend in the motor paths of the cord to play upon the anterior horn cells governing the muscles in question Such impulses probably augment tone and are balanced by others passing down the pyramidal tracts to the anterior horn cells and inhibiting tone It is thus evident that the alterations in tone which muscles exhibit may be due to influences operating in a variety of ways We are of course familiar with the major tone changes which accompany peripheral nerve and central nervous lesions They are conspicuous and easy to appreciate It is much harder to arrive at conclusions as to the alterations in tone which attend fatigue The difficulty arises from the impossibility of making direct measurements of tone At the present time such measurements are either in terms of very inexact opinions as to the relative plasticity hardness or tension of muscles under consideration or else they are expressed through alterations in the activity of reflex arcs Careful study of the knee jerk is often used as

a product of muscular contraction, but that it is actually part of the machine. Apparently every muscular contraction is accompanied by lactic acid production. Unless work is extremely severe this acid is not lost but is held by the muscle for future use. In extreme work there is actual loss of lactic acid through excretion in the urine[1]. In addition to lactic acid other substances such as carbon dioxide and acid potassium phosphate carrying hydrogen ions are freed during muscular contraction and may be of importance in the causation of fatigue[13]. The so-called fatigue products have had a certain degree of popularization owing to the experiments of Weichardt and his purported demonstration of fatigue toxin and antitoxin. It has been impossible however to repeat his work and there is no good evidence that nitrogenous substances are either produced as a result of fatigue or have any part in its development.

Lee[14] in a series of experiments perfused isolated muscles adding a variety of substances to his perfusate, and was able to show that depression could be produced very readily. His experiments however though often quoted should not be regarded as identifying any fatigue substance. They lead to little save the fact that any increase in acidity is unfavorable for muscular work. Very recently Hastings[15] utilizing modern methods obtained the following results:

"(1) Exercise produced a diminution of the bound carbon dioxide of the blood plasma. The depletion however, did not progress to such a point that the reaction of the plasma was significantly altered. (2) The lowering of the bound carbon dioxide was a function of the rate and the amount of exercise. (3) The rate at which the bound carbon dioxide returned to its original value was related to the amount of exercise. (4) The urine of men engaged in manual labor tended to be of a slightly higher degree of acidity than that of men at rest. This statement could only be made of the class as a whole and could not be reliably applied to individuals without accurate knowledge of their diets. (5) The urine of physically strong men was regularly slightly more acid after work than before; the urine of physically weak men showed wide variations in its reactions from day to day. (6) When the muscular activity was such that the subject was intensely fatigued there was invariably an increase in the hydrogen ion concentration of the urine."

These demonstrations make further measurements of the same sort highly desirable but they demand a degree of dietary control which makes them hardly applicable for practical use. The prospect of attaining any simple test in the blood or urine which would indicate fatigue development seems very remote at the present time.

Working mammalian muscle is extremely dependent upon blood supply. The rapid utilization of oxygen must be met by steady replenishment

Bodily work with its accompaniments of heightened blood pressure and increased heart rate means invariably more blood per minute through the active muscles. That the blood stream also supplies combustible material in the form of dextrose is probable but how far the immediate nutrition of working muscle is important for fatigue prevention is not known. The fact that easily assimilable carbohydrate food is a most efficacious agent in carrying men through exhausting work has been frequently demonstrated but the rapidity with which such material is actually used has not yet been estimated accurately. In the same way very small amounts of alcohol which will be burned at once may prove to be sources of muscular energy of some value but in this case the reverse result will appear if the dosage is great enough to produce any nervous effects.

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While the simple arc so described is fundamentally responsible for tone portions of the central nervous system may also influence it. Thus some of the impulses flowing in from muscle may ascend the cord to other reflex centers vestibular nucleus cerebellum red nucleus or corpus striatum and descend in the motor paths of the cord to play upon the anterior horn cells governing the muscles in question. Such impulses probably augment tone and are balanced by others passing down the pyramidal tracts to the anterior horn cells and inhibiting tone. It is thus evident that the alterations in tone which muscles exhibit may be due to influences operating in a variety of ways. We are of course familiar with the major tone changes which accompany peripheral nerve and central nervous lesions. They are conspicuous and easy to appreciate. It is much harder to arrive at conclusions as to the alterations in tone which attend fatigue. The difficulty arises from the impossibility of making direct measurements of tone. At the present time such measurements are either in terms of very inexact opinions as to the relative plasticity hardness or tension of muscles under consideration or else they are expressed through alterations in the activity of reflex arcs. Careful study of the knee jerk is often used as

indicating alterations in tone, this reflex being dependent on the integrity of a simple sensory motor arc and disappearing with tone when the arc is interrupted Both as a result of fatigue and also as a result of under feeding the knee jerk is both slowed and rendered less extensive Unfortunately the apparatus required to bring out such facts renders study of tone through measurement of reflexes a complicated laboratory maneuver and makes it unavailable for group use in industry There is little doubt that did we possess some easily applied and accurate measure of muscle tone we should have a valuable means of detecting fatigue and foretelling physical fitness for various tasks *

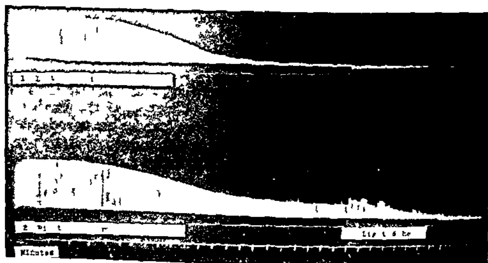


Fig 6—Fatigue curves in circulated and non circulated muscles

Characteristics of Fatigue Curves Under Laboratory Conditions

Simple Preparations in Animals and Individuality in Neuromuscular Reactions

In Tracing 1 Fig 6 we have an illustration of the simplest type of fatigue curve that made by direct stimulation of the isolated gastrocnemius muscle of the frog *Tracing 2* of the same figure displays the fatigue curve written by the opposite gastrocnemius muscle of the same animal under conditions precisely similar to Tracing 1 save that the circulation has

* Ryan Jordan and Yates in the American Journal of Physiology 1919 XLIX 131 describe apparatus for measuring tone alterations and mention results gained in industry Full details are however withheld

been left intact up to the point where the ligature is marked as tied This last curve shows most of the characteristics displayed by the body in complex types of work There is an initial period of increasing efficiency during which the muscle is apparently "warming up This is followed by a period of maximum efficiency and then there is a period of progressing fatigue until the point A is reached It is clear that from this part of the curve to the point of ligation the contractions are diminishing rather slowly and it is safe to say that had the ligation been omitted a stage would have been reached in which the height of contraction ceased to diminish This stage is spoken of as the fatigue level When it is reached the muscle has attained a state constantly exemplified by the heart and diaphragm in which rate of stimulation load lifted supply of oxygen and removal of metabolic waste products are all in equilibrium Such a fatigue level is exceedingly easy to di rupt Thus an injection of adrenin will at once cau e an increase in the height of contr iction expressing the lowered threshold of the muscle cells for stimulation Similarly the first effect of cutting off the circulation has been slight increase in extent of contr ic ion possibly due to a sudden concentration of waste or fatigue products which like many other substances may precede their depressing effects by actual stimulation A decrease in load a change in the rate of stimulation a sudden change in temperature and many other influences will disturb the fatigue level but if the new influence is of such nature as to act ste dily and the circulation remains good another fatigue level appears It is not easy indeed it may almost be said to be impossible through exercise alone to reduce a well circul ited muscle in warm or cold blooded animals to a condition of complete fatigue where no contraction of any sort occurs Some other influence must be brought to play upon the preparation in order to attain such a result

This concept of the fatigue level is an important one The height at which such a level can be maintained reflects in a striking way the power and efficiency of the muscle tested Such level appear very readily in work with the ergograph and present one of the few fields for study still open in the use of this historic instrument

Finally no extended experience with even the simplest type of fatigue curves written under the best laboratory conditions can fail to impress the observer with the differences in form which identical muscles from different animals display Companion muscles from the same animal will check one another very precisely both in the form of the fatigue curve and in the total amount of work done Mo o[16] noted differences in the ergographic curves from different individuals and found that neither practice nor ill health altered the es ential form of the curves so that after a certain period of experience it was possible in many in tance to

identify the individual writing the curve from the tracing alone. In such experiments the central nervous system is, of course, involved but one finds much the same type of variation in curves made through stimulation of muscle alone and is led to the conclusion that variations in the manner in which individuals tire out are conditioned more by variations in irritability and contractility of their muscles than by variations in such nervous control functions as their power of will. Thus with the ergograph one subject practically from the start slips steadily into fatigue while another maintains a high level of contraction over a long period and goes suddenly to pieces. In both instances there has been the strongest possible effort toward maximum accomplishment but the manner in which the simple task is carried out varies considerably and at the present time the responsibility for this variation would seem peripheral, in the myoneural junctions and in the muscle cells themselves rather than in the brain and spinal cord.

One of the interesting medical contributions of the war lies in the realization that there is a group of individuals whose distinction as hospital patients is confined to the fact that they fatigue with abnormal ease. Lewis[17] describes such cases as follows:

When a healthy man takes exercise and this exercise is sufficiently stressful or prolonged he becomes aware at the time of the effort or after it has ceased of certain symptoms and he presents certain physical signs. The most notable of his symptoms is breathlessness, a symptom which comes during the exercise and continues with diminishing intensity for a variable period afterwards. During the exercise consciousness of the heart beat may come, giddiness or actual faintness or fatigue may be added. At the cessation of the exercise aching of the limbs, tremulousness and exhaustion are experienced; at a later period stiffness of the muscles, a feeling of lassitude and sometimes actual malaise and tremulousness are noticed. In cases of extreme effort pain over the precordial region at first aching but exceptionally more violent and widespread may be felt. During the period of exercise the heart rate and blood pressure are raised, the alae nasi are dilated, the accessory muscles of respiration are brought into action to increase the tidal flow of air. To these physiological symptoms and signs briefly described as a group I apply the term physiological syndrome of effort. The term is used as a convenient description of the chief changes subjective or objective which are manifested by the human body in its reaction to exercise and one purpose in introducing it is to emphasize a working hypothesis at which I have arrived, namely that a large number of patients, especially soldier patients, who come under observation, report sick or are regarded as sick because they notice or present such a series of symptoms and signs. When I use the term effort

syndrome I have in mind the symptoms and signs which follow exercise in health but I believe that I recognize the same or a very similar group of symptoms and signs in a large class of patients in ill health In patient of this class if no signs of disease are anywhere discovered I say that they suffer from the effort syndrome The difference in symptomatology which exists between health and this form of ill health is largely a difference in degree the gauge is the amount of work which performed in a given space of time will provoke the symptoms Symptoms produced in normal subject by excessive work are produced in the patients by lesser amounts the smaller the amount of work required the more severe the malady Naturally there is no sharp line of division there is in a large group of patients a perfect grading from the healthy man to him who is seriously unwell *

We have already spoken of the variation in manner of working which the same muscles from different individuals exhibit and of the fact that this variation probably does not have its locus in the central nervous system but in the myoneural junctions and in the muscle cells themselves Cases of individuals who fatigue abruptly such as Lewis describes may represent an enormous exaggeration of this individual variation but it is hard to believe that the pathological physiology of such persons is altogether separated from the central nervous system Many such patients have always been physically and mentally inferior to their fellows others date their display of the effort syndrome" from some severe accident or shock It is not easy in such instances to rid the mind of a mental or central nervous as well as a peripheral locus for the changes which have occurred in the neuromuscular abilities of the individual

Neuromuscular Fatigue in Man

The simplest type of laboratory fatigue curve is that written with the ergograph of Mosso[16] Curves of this sort ordinarily exhibit an initial rise in efficiency a brief period of maximum efficiency and an eventual decline If appropriate apparatus is employed this decline will be arrested at a definite fatigue level We need not comment upon the general shape of such curves except to say that data gained from a variety of neuromuscular operations and plotted upon coordinate paper as a rule produce curves identical in form with the familiar ergographic tracing

The ergograph has been largely supplanted as a laboratory instrument owing to the fact that its use involves too high a degree of training and cooperation upon the part of the subjects employed In spite of this the

* Those interested in material bringing out the importance of the effort syndrome in industrial life will find valuable material in the following articles Meredith F L Boston M & S Jour 1919 CLXXXI 734 White P D Jour Am M Ass 1920 LXXIV 580

actual results obtained by Mosso and his school are of great importance in certain relations. Thus, the fundamental observation of Maggiora[18] as to the rest period necessary to repeat a given amount of work will always be significant. Maggiora first proved that two hours of complete rest are required before every trace of fatigue disappears from the flexor muscles of the fingers after they have been exhausted in the ergograph. If he diminished this period, for example, by allowing only one hour instead of two to elapse between one series of contractions and another, the muscle, being insufficiently rested, naturally did less work. Now it might be thought that if the work were reduced by one half the period of repose might also be reduced in the same proportion. But by experiment it was found that the period of repose might actually be reduced not to half but to a quarter, that is to say, if thirty contractions are required to exhaust a muscle completely, the period of repose necessary after fifteen contractions is only half an hour.' Fatigue moreover does not increase in proportion to the actual work accomplished, that is, to the efficiency of the working individual. If the work is calculated by adding together the successive heights through which the weight has been raised, we find that the work done during the first fifteen contractions is much greater than that done during the second. Yet in this last group we find the major portion of the muscular breakdown. In each of the experiments we are now discussing Maggiora began in the morning and continued observations until evening, a tracing of fifteen elevations being repeated every half hour. And the fact that these tracings were every one equal in height shows that the period of repose was sufficient for the muscle. It appears therefore that if muscular energy is not completely exhausted, that is to say, if the final efforts are not made, fatigue is much less and the muscle is able to perform more than double the amount of mechanical work which it would do if worked to the point of exhaustion, even with the most favorable conditions for repose.

Ash[19] has employed the ergograph to illustrate an interesting feature of fatigue which has already been commented upon. In Fig. 7, as the legend indicates, the bottom one of the three tracings is the conventional ergographic curve. The two other curves are written by two other fingers of the same hand during the same period. Note their gradual increase in height as fatigue develops in the lower curve. This means that as the muscle cells in the middle finger tracing are gradually eliminated from action other closely associated muscles are thrown in, with a resulting clumsiness and incoordination. Ash explains such a phenomenon on the ground that as fatigue develops the organism loses power to inhibit undesired action. It seems more probable that as fatigue progresses and the muscle units which should properly accomplish the desired task are eliminated

from participation in the muscular act through ri e in thresholds allied muscles not so directly useful but still capable of assisting in the task are thrown into activity In such terms we should expl in the incoordination which accompanies fatigue in terms of an irradiation in the motor cere brum The experiments of Ash in spite of our disagreement with his explanation of the results are of importance in that they point out a val uable means of testing fatigue which h is not been utilized to sufficient degree

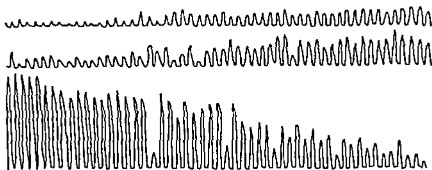


FIG 7 —Ergographic records illu trating the effect of fatigue upon control (From Ash s *Fati ue and Its Effects upon C ntrol*)

THE REACTIONS ACCOMPANYING MUSCULAR WORK [0]

Circulation

In rest the heart of a normal adult di charges from three to six liters of blood per minute This amount may be augmented to twenty two liters per minute as a result of hard exercise Several factors combine to accomplish the increase

(a) *Greater Diastolic Filling* —One of the most important elements in accomplishing greater cardiac output is greater delivery of blood to the heart and this must of course be followed by successful management of the incre ised load In the past it has been thought that the heart was capable of a type of receptive relaxation that there was a reduction in the tone of the cardiac muscle which occurred under certain circumstances and which determined the degree of diastolic filling The heart does oper ate at different sizes but according to the present view the size seems to depend wholly upon the amount of blood delivered by the venae cavae and not upon tone changes in the sen e noted above Starling[21] has

brought out the fact that the energy of contraction in healthy cardiac muscle as in the case of skeletal muscle is a function of the length of the muscle fiber Thus if the venous inflow is suddenly great and the ventricles widely filled it is an essential feature of healthy cardiac function that the next contraction must be correspondingly increased This is the law of the heart and its operation coupled with an increase in rate makes the organ meet the demands of exercise very perfectly Starling has pictured the adaptation as follows

Thus if a man starts to run his muscular movements pump more blood into the heart so increasing the venous filling while the central nervous system by contracting the arteries of the abdomen increases the peripheral resistance raises the arterial pressure and forces all the available blood through the active muscles As a result the heart is overfilled during diastole and is impeded from emptying itself in systole its volume both in systole and diastole enlarges progressively until by the lengthening of the muscle fibres so much more active surfaces are brought into play within the fibres that the energy of the contraction becomes sufficient to drive on into the aorta during each systole the largely increased volume of blood entering the heart from the veins during the diastole

In these circumstances therefore the heart is dilated But in a healthy individual this condition is only temporary A rise of arterial pressure produces a more abundant flow of blood through the vessels supplying the wall of the heart and this increased supply of oxygen and food stuffs improves the physiological condition of each muscle fibre so that at each contraction it is able to concentrate a larger number of active molecules on each unit of active surface than it could previously The physiological condition or what we are accustomed to speak of as the tone * of the heart is thereby improved and the heart gradually returns to its normal volume even though it is doing increased work It is only when the heart is fatigued or diseased that this secondary improvement fails to appear

* The word tone has been often used in connection with the heart though a clear conception of its significance has generally been lacking When on opening the chest the heart is found to be dilated it is often said to be lacking in tone on the other hand if the heart is found small and evidently emptying itself completely during systole and dilating only slightly during diastole its tone is said to be increased But the state of dilatation of the heart may be merely a question of the amount of blood entering it from the veins A contracted heart may be in a bad condition and a dilated heart may be in a good condition It is clear now that the word tone is properly employed as synonymous with physiological condition or fitness of the muscle fiber and its measure is the energy set free per unit length of muscle fiber at each contraction of the heart A heart in good condition i e one with a good tone will carry on a large circulation against a high arterial pressure and nearly empty itself at each contraction while a heart with a defective tone as is the case when it is tired can carry on the same circulation but only when its fibers at the beginning of contraction are much longer i e when the heart is dilated In the latter case the output of blood will be the same as the former but both the systolic and the diastolic volumes of the heart will be increased

Then we find that the heart remains dilated over the whole period of increased work and if the work is prolonged this dilatation may become permanent.*

The output of the healthy heart in each beat thus depends upon the degree of diastolic filling and this in its turn is mainly dependent upon the amount of muscular activity. It is apparently true that the venous massage which active muscles bring about is the main factor in driving blood toward the heart. The series of phenomena attending work are thus beautifully adapted to get more blood to them. Their activity at once throws this larger supply back to the heart which if healthy immediately returns the new influx and since increased respiration also accompanies exercise the active muscles are assured of an adequate supply of well oxygenated blood and a constant removal of carbon dioxide and waste products.

The cardiac output which accompanies exercise depends also upon

(b) *Increased Rate.*—Several factors combine in producing this and it is hard to tell in any given instance which one dominates. First of all there is a reflex reduction in vagal tone, that is, the vagus center which has been holding the heart in constant slight check is inhibited. Just how this reflex is brought about we cannot say but it is probably responsible

TABLE I

Group	Number of Cases	Lying Average	Standing Average	Hopping Average	Afterward Average
50–59	2	55	75 ± 6.5	87 ± 12.1	63 ± 9.5
60–69	193	65	85 ± 9.4	95 ± 13.9	[illegible]1 ± [illegible]4
70–79	305	[illegible]4	91 ± 9.5	103 ± 12.3	8[illegible] ± [illegible]9
80–89	358	83	98 ± 9.4	111 ± 1[illegible].9	87 ± 8.4
90–99	[illegible]8	94	108 ± 11.0	1[illegible]0 ± 12.5	95 ± 9.3
100–109	3	102	114 ± 9.9	128 ± 9.0	104 ± 8.5
110–119	7	114	125 ± 13.4	143 ± 9.[illegible]	116 ± 5.2

AVERAGE AND STANDARD DEVIATION OF THE PULSE

RATE REACTIONS OF 1,000 NORMAL RECRUITS

for the almost instant increase in rate which accompanies exercise and it seems that the motor cortex is involved since there is no initial acceleration of the heart when the limbs are moved passively. Following upon the vagal release which accounts for the first increase in heart rate there is an increase in accelerator tone which operates for a varying length of time to hold the rate high and which in its turn is probably ordinarily supplanted by the effect of increased temperature which results from the exercise. The degrees of pulse acceleration and blood pressure increase which

attend exercise in normal individuals depend very much upon the severity of the exercise and apparently the usefulness of such observations in detecting subnormal individuals depends more upon the rate at which the tested person returns to normal when exercise ceases, than the degree of cardiac acceleration or blood pressure increase accompanying the exercise Addis", in connection with examinations of soldiers, has given convenient directions and normals (see Table 1) for determining the pulse increase in exercise

"1 The recruit lies on his back without moving for fifteen minutes The pulse rate is then taken If the rate exceed eighty eight per minute he lies still for another fifteen minutes before the pulse is counted

This is called the basal pulse rate

2 The recruit rises from bed and stands up While he is doing so the observer's fingers should be on his wrist so that he can begin to count the pulse rate as soon as the patient is erect He counts for fifteen second only

This is called the standing pulse rate

"3 The recruit is then directed to hop one hundred times on the left foot at a rate of about two hops to the second If no one counts for him he should be told to count the hops himself

Immediately on the completion of the one hundred hops the recruit lies on his back in bed and the pulse rate is counted for the first fifteen seconds after he lies down

"This is called the hopping pulse rate

4 The recruit continues to lie on his back and exactly two minutes after the completion of the hopping count the rate is taken again for fifteen seconds

This is called the after pulse rate

The count should begin when the second hand covers one or the other of the five second divisions of the second hand dial This may necessitate waiting almost five seconds in some case but it is generally more accurate than attempting to gage the position of the second hand between the divisions

Some find it an advantage to set the minute hand of the watch on an hour division on completing the hopping count in order to make it easier to determine when the two minute interval has been completed

"Care must be taken to see that the minute hand of the watch does not obscure the reading of the second hand dial

Other figures of similar type together with figures for blood pressure increase will be found in an article by Cotton Rapport and Lewis (Heart 1915–1917 VI 269) in the monograph Human Vitality and Efficiency under Prolonged Restricted Diet (Publication No 280 Carnegie Inst, Wash

1919) where use is made of different types of exercise and in a recent article by Percy M Dawson (Am Jour Physiol 1919 L 443)

Respiration

In the preceding section we have summarized very briefly the circulatory changes which are the indispensable accompaniment of exercise They form the link between the source of oxygen and the means of elimination of carbon dioxide in the lungs and in the actively metabolizing muscles Muscle possesses a certain amount of fat and carbohydrate which can be transformed into work and heat and in the liver and fatty depots of the body other stores of oxidizable material are found which are drawn upon when needed It used to be thought that the oxygen necessary for the oxidation of these substance and consequently for their utilization in muscular contraction was at least in part stored within the muscle cells but this is not the case The oxygen required for such reactions is brought by the blood and is supplied as it is required and never in excess Muscle thus differs from the fire which burns brighter under the blast of the bellows The increase in oxidation which is a necessary factor in muscular work is itself in the last analysis the cause of the larger oxygen supply and the means of getting rid of carbon dioxide Muscular work thus at once increases the oxygen supply of the muscles involved and so close is the relationship between the two that the consumption of oxygen per minute varies directly with the work done in the same time In order to obtain the oxygen required by working muscle respiration must increase and the blood flow through the lungs and muscles must keep pace with the requirements of the moment The question of blood flow increase has been dealt with in a previous section

As a result of the work of Haldane[3] and his students we have been led to believe that the normal stimulus for the respiratory center is found in the hydrogen ion concentration of the blood Henderson[4] has described the reactions through which the hydrogen ion concentration of the blood is regulated, and it is well to repeat his concise summary

The hydrogen ion concentration of the body has been seen to depend upon the ratio $\frac{H_2CO_3}{NaHCO_3}$ Acid reaction with this system causes a diminution of the denominator and an increase in the numerator of the fraction the value of the fraction increases and with it the hydrogen ion concentration Hereupon the lung reduces the value of the numerator by diminishing the concentration of carbon dioxide in blood and alveolar air the value of the fraction is restored more or less exactly to its original value and with it the concentration of the hydrogen ion But the denominator

is still below normal. To offset this there occurs on the one hand a production of ammonia which takes the place in the urine of alkali existing as salt in the blood. This alkali recombines with carbonic acid forming bicarbonate and thus increasing the denominator. On the other hand the kidney removes less alkali in combination with phosphates than exists in this state in the blood. This alkali, too, helps to regenerate sodium bicarbonate and thus to increase the denominator. Both of these processes are so regulated that the denominator is restored to normal. The concentration of carbonic acid responds through the activity of the respiratory mechanism and the organism returns to its normal state.

These processes of course go on simultaneously and not in succession. They are, moreover, far less simple than such an analysis admits; for on the one hand the interaction of phosphates and proteins has not been fully described, and on the other hand many of these variations influence other conditions and processes in the organism."

If we view the matter as simply as possible the increased breathing accompanying exercise is incident in the first place upon an added output of carbonic acid which has its principal effect in increasing the numerator of our fraction. In other words, the hydrogen ion concentration of the blood has been very minutely added to by means of carbonic acid and *the increased breathing which results in a better supply of oxygen for the active muscle* is clearly incident upon the heightened oxidation essential for the accomplishment of work.

Recent observations indicate another possible cause for the respiratory increase accompanying carbonic acid additions to blood. Hooker[25] and his associates found that dogs in whom the respiratory center was perfused with blood containing different acids but of the same hydrogen ion concentration showed maximum respiratory response when carbonic acid was used. The explanation of this fact lies, as these investigators point out, in the possibility that carbon dioxide, in addition to its property of slightly increasing the hydrogen ion concentration of the blood, possesses also power to lower the threshold of the respiratory center so that for a *given hydrogen ion* concentration the breathing is much amplified.

Haldane[26] *recently* and also Loevenhart[27] have maintained that oxygen lack also may stimulate the respiratory *center*, but whether this stimulus is due specifically to absence of oxygen or whether it is due to other phenomena incident upon oxygen want is not known. In addition to the contribution of carbonic acid which we have seen to be particularly potent *in* stimulating respiration, exercise, if pushed far, may result in *the* delivery of lactic acid from muscle to the blood stream. This substance will not only add directly to the hydrogen ion content of the blood but will also decrease the *denominator* of our fraction. It is thus probable

that during severe exercise the heightened respiration is the result of the addition of non-volatile acids to the blood as well as of the carbonic acid which we have discussed as the main source of respiratory stimulation.

It is not possible to provide any figures giving the normal increase in respiration with standardized amounts of exercise. A variety of statements indicate the general extent of the change. Thus Bainbridge[9] remarks: "The range of pulmonary ventilation is very large and a short period of violent exercise such as 100 yard race may lead to a ventilation of *150 litres per minute or even more*. . . . During less severe work which can be carried on for some time the pulmonary ventilation does not usually exceed 100 to 150 litres per minute and this figure is probably near the limit reached by most individuals during severe continued work." Peabody[25] has related the vital capacity of the lung, that is, the volume of air which can be expired after the deepest possible inspiration, and the dyspnea of exertion. He presents the normal figures given in Tables 2, 3 and 4.

Peabody has shown that in heart disease there is a close relationship between dyspnea and the vital capacity of the lung. "Thus, in general, patients with a vital capacity of ninety per cent or more of the normal standard adopted for their sex and height have little or no tendency to dyspnea. Patients with a vital capacity of from seventy to ninety per cent of the normal become short of breath on unusual exertion and must lead a restricted life, although many of them can do light work. Patients with a vital capacity of from forty to seventy per cent of the normal are much more limited in their activities. They become dyspneic on moderate or slight exertion, are rarely able to work and frequently suffer from cardiac decompensation."

Peabody has shown also that in other diseases in which mechanical conditions interfere with the movements of the lungs the tendency to dyspnea corresponds closely to the decrease in vital capacity. Unfortunately no similar studies have been made upon workmen whose occupations have resulted in extensive lung changes. It has been shown that the vital capacity of a few individuals with advanced silicosis is reduced, and this reduction must certainly be accompanied by failure to meet the respiratory requirements of severe exercise. It is very probable that the functional severity of the changes readily demonstrated by the X-ray in the pneumokonioses could be correlated with alterations in vital capacity and with the tendency of inspired carbon dioxide to produce dyspnea. Observations such as these would do much to determine the real capacity for work which the individuals possess who have labored over long periods in dusty surroundings, and they would also do much toward separation of the pathological possibilities offered by the various dusts.

Table 2

Group	Number Studied	Height in Feet and Inches	Normal Vital Capacity Cc	Number Within 10 Per Cent of Normal	Highest Vital Capacity	Lowest Vital Capacity	Highest Per Cent	Lowest Per Cent	Number Below 90 Per Cent of Normal
I	14	6 +	5 100	9	7 180	5 030	141	99	0
II	44	Over 5 8½ to 6	4 800	41	5 800	4 300	121	90	0
III	3	5 3 to 5 8½	4 000	31	5 080	3 450	127	86	1

The Vital Capacity of the Lungs of Normal Males

Table 3

Subject	Height in Feet and Inches	Vital Capacity Cc	Vital Capacity Per Cent of Normal	Training
G E H	6 3/	7 180	141	Track team football and crew 4 years
P W	6 2¼	6 100	120	Cross country runner 4 years
P N N	6 2	6 100	120	Basketball and track team 4 years
H M R	6 1⅛	6 000	118	Crew much general athletics
A M G	6 1¾	6 200	122	Hockey team football team crew
H J	5 11½	5 800	121	Cross country runner
F M C	5 11	5 410	113	Football and track teams
N R	5 11½	5 530	115	Football and track teams
F C H	5 10½	5 530	115	Cross country runner 4 years
C R M	5 6	4 690	118	Football team 3 years track team 4 years

The Vital Capacity of the Lungs of Ten Athletes

Table 4

Group	Number Studied	Height in Feet and Inches	Normal Vital Capacity Cc	Number Within 10 Per Cent of Normal	Highest Vital Capacity	Lowest Vital Capacity	Highest Per Cent	Lowest Per Cent	Number Below 90 Per Cent of Normal
I	10	Over 5 6	3 275	5	4 075	2 800	124	86	
II	13	Over 5 4 to 5 6	3 050	9	3 425	2 660	112	88	2
III	21	5 4 or less	2 825	16	3 820	2 500	135	89	1

The Vital Capacity of the Lungs of Normal Females

Haldane[29] has discussed the very interesting question of the effects of siliceous as opposed to other dusts the former being an extremely potent producer of pulmonary fibrosis He remarks with surprise upon the fact that lung injury and miners phthisis are practically unknown in the Cripple

Creek district of Colorado though the rock worked is very rich in silica As a matter of actual fact the dust in this region apparently does do the damage which he expected but since the work is heavy for a normal man just as soon as fibrosis makes any progress the individuals affected move out being unable to support heavy work at such a high altitude in the face of any handicap whatsoever Haldane[3] discusses other possible relations of respiration to work under industrial conditions in connection with the carbon dioxide content of the air Thus in many mining operations the carbon dioxide content of the air tend to become high It is found that a percentage of one 1 consonant with heavy manual labor but that further increases necessitate such heavy breathing as to render high efficiency quite impossible Similarly in deep sea diving and in caisson work the carbon dioxide must be kept low through forced ventilation if heavy work is to be accomplished Clearly in any of these instances men with circulatory embarrassment or men whose lungs have begun to show the fixation characteristic of the pneumokonioses must be at a decided disadvantage from the start and owing to the fact that dyspnea on slight exertion is an unpleasant and insistent handicap men so affected will drift inevitably toward other types of work

Metabolism

The working individual obtains energy for his task from increase in his metabolism Many investigations have concerned themselves with the factors involved in this increase * In the foods which we ingest there are three sources of available energy namely carbohydrate fat and protein Protein metabolism is not affected during mechanical work unless there is coincident carbohydrate starvation These facts should not cause one to neglect the equally important fact that if carbohydrate is not fed and if opportunity is given through a course of muscular work to exhaust the carbohydrate stored in the body protein will be burned and may become practically the sole source of bodily energy This is however a matter of little consequence in practical considerations of work since it is improbable that the protracted work of industry could be accomplished on such a basis On the other hand excessive protein ingestion is not essential for the maintenance of physical power †

A very useful summary upon this subject is found in Lusk G The Elements of the Science of Nutrition Philadelphia 1917 309

† The recent and comprehensive report upon the relation of a restricted diet human vitality and efficiency contains much material bearing upon the nutritional aspects of work and fatigue See Human Vitality and Efficiency under Prolonged Restricted Diet by Benedict F G Miles W R Roth P and Smith H M Publication 280 Carnegie Inst Wash 1919

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THE VITAL CAPACITY OF THE LUNGS OF NORMAL MALES

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Subject	Height in Feet and Inches	Vital Capacity Cc	Vital Capacity Per Cent of Normal	Training
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THE VITAL CAPACITY OF THE LUNGS OF TEN ATHLETES

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II	13	Over 5 4 to 5 6	3 050	9	3 425	2 660	112	88	2
III	21	5 4 or less	2 825	16	3 8 0	2 500	135	89	1

THE VITAL CAPACITY OF THE LUNGS OF NORMAL FEMALES

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The results of the work of Benedict and Cathcart[30] upon an individual who rode a stationary bicycle to the point of exhaustion show that the heavier the muscular activity the more severe the draft upon the carbohydrate material in the body with the eventual probability that a large part of the stored carbohydrate is used up. It is not possible to state just how far stored fat is used in such experiments as these but it is certainly possible to replace carbohydrate by fat for the furnishing of mechanical power. It seems true however that the easily assimilable carbohydrates offer the readiest form of energy yielding material and their ingestion is most apt to counteract the development of fatigue.

A further point of importance is found in the influence of training upon the economy with which muscular work is accomplished. Table 5 taken from Lusk's Science of Nutrition (p. 332) shows the greater excretion of carbon dioxide in the untrained as against the trained individual

TABLE 5

Place	Altitude in Meters	Incline of Road in Per Cent	CO_2 Excretion per Kgm of Work	
			Untrained	Trained
Brienz	620	17.29	2.430	2.103
Gornergrat	2 987	19.3	2.711	2.268
Brienz	690	19.0	2.251	2.063
Gornergrat	3 021	19.3	2.445	117

EFFECT OF TRAINING ON METABOLISM

during mountain climbing. Other physiological facts do not indicate that this difference expresses a greater economy of action in individual muscle cells but indicate rather that the trained individual achieves his results with utilization of the minimum number of cells required to bring about the particular activity. He does little or nothing which is unessential.

Benedict and Cathcart[30] have also shown that the efficiency of the human organism varies both with the rhythm and the load involved in the tasks studied. Table 6 a section of one of their tables shows the decrease in efficiency experienced in increasing the speed of pedalling a stationary bicycle and Table 7 also a part of one of their tables, indicates the decrease in efficiency on the part of the human machine when the load in this same work is increased by increasing pressure from a magnetic break.

There is no doubt that all industrial tasks entail similar variations in efficiency in accordance with the speed at which they are performed and the load which must be carried. It has been the object of scientific management to find these relations between load and speed for each task. The

TABLE 6

Date	Revolutions per Minute	Heat Equivalent of External Work Per Minute	Net Efficiency
191	Effective Work 1 35 Calories		
April 8	70	1 33	23 0
	1	1 35	23 3
	1	1 36	23 0
Average 3 periods	71	1 34	23 1
February 26	94	1 29	20 4
February 9	102	1 35	8 1
	104	1 35	17 0
	107	1 35	15 8
	108	1 37	17
Average 4 period	105	1 35	17 0

EFFICIENCY OF SUBJECT M A M COMPARED AT DIFFERENT SPEEDS WHEN THE AMOUNT OF EFFECTIVE MUSCULAR WORK PER MINUTE REMAINED CONSTANT (ERGOMETER II)

(Basal values obtained with subject lying on couch)

TABLE 7

Subject	(a) Increase in Magnetization from—	(b) Increase of Total Heat	(c) Increase of Heat of External Work	(d) Efficiency $\frac{c \times 100}{b}$
	amp	*cals*	*cals*	*p ct*
M A M	0 5 to 0 95	144	49	34 0
		140	44	31 4
		48	44	29 7
		195	48	24 5
		185	48	25 9
		191	48	25 1
M A M	0 5 to 1 1	158	43	27
		163	43	26 4
		168	43	25 6
		2 5	6	2 5
M A M	0 5 to 1 25	185	52	28 1
		176	52	9 5
		184	53	28 8
		331	7	23 3
M A M	0 5 to 1 5	365	98	26 8

EFFECT OF INCREASED LOAD ON BODY EFFICIENCY WITHOUT REGARD TO VARIATIONS IN SPEED (AMOUNT PER HOUR)

difficulty which is found in relating such studies as the efficiency engineers have published to the physiological data here presented lies in the fact that in both instances we lack figures upon what we may speak of as sustained efficiency Thus one may in the laboratory obtain excellent curves portraying the efficiency of the individual in brief tasks and in a similar way the efficiency engineer may introduce methods which disclose an enormous increase in output over several months time but in neither case have we any measure of the final physiological state of the individual We do not know whether physical efficiency, in terms of even one year's time can be sustained at the somewhat artificially developed level *

Practical Methods of Estimating Fatigue

Attention has already been drawn to one of the methods for gauging fatigue namely by means of the ergograph Such an instrument can be used in two ways First one may from a condition of rest write characteristic fatigue curves In such experiments we portray the development of fatigue in a simple task under standardized conditions Secondly having made many fatigue curves of the type just mentioned and having thus in hand a measure of the normal capacity of the individual we may use the ergograph at the close of other tasks to show the extent to which the subject has been rendered unfit by the work under observation Mosso[16] the originator of the ergograph did both of these things studying the character of ergographic curves under normal conditions and using such curves as indicators of the harm done by many types of physical and mental stress Mosso has been followed by a host of other experimenters employing the ergograph various types of dynamometers, etc and testing many sorts of mental and physical work The reader wishing a list of such methods is referred to the Manual of Mental and Physical Tests, by G M Whipple The limitations of this article permit the discussion of but a few of the most recent and the most practical means of estimating fatigue

Sensations of Fatigue

There is apparently no method of judging fatigue which is so completely misleading as the report of the individual as to how "tired he is Interest emotional excitement of many sorts may cause a neglect of the

* Those interested in measurements of metabolism in simple types of industrial work will find data in the following articles Amar J Jour de physiol et de path gen 1913 XV 62 and 79 Waller A D Jour Physiol (Proc Physiol Soc) 1919 LII xlviii and lix Greenwood M Hodson C and Tebb A E Proc Roy Soc Lond 1919 XCI Series B 6

accumulating effects of fatigue with eventual complete breakdown It is necessary to make this warning very emphatic in relation to industrial fatigue since investigators should be taught to judge the accumulation of fatigue not in terms of the opinions of either employees or employers but on the basis of the most objective data available

Martin s Spring Balance Test

For the purpose of estimating both the extent of the damage and the degree of improvement in cases of poliomyelitis Martin[31] has devised a series of very simple tests which are readily applicable to industrial workers as well as to the more easily handled subjects of the hospital and laboratory The American Committee for the Study of Industrial Fatigue during the war made use of this test upon a large number of workmen but as yet their results have not been published Smith[3] has used Martin s test in the study of soldiers suffering from the effort syndrome and gives data relative to its value Martin and Rich[31] give the following concise description of the entire procedure

Apparatus Required —An ordinary flat faced spring balance with a scale capacity of 200 pounds marked in 2 pound units equipped with a self registering index (There are scales on the market with self registering indices but these are heavier than desirable We have found it satis factory to fit up an ordinary scale in our own shop with a simple device) A stout wooden handle is attached by a swivel to the upper end of the scale and a loop of stout leather one and one fourth inches wide and thirty inches in circumference is attached by another swivel to the lower end of the balance

A stout table six and one half feet long and two and one half feet wide with a cleat secured firmly across one end A cushion on which the subject s head may rest should be provided with this table

An upright post four inches square and at least six and one half feet high so placed that it is surrounded on at least three sides by ample space Some form of hand hold is provided by which the subject may steady himself as he leans against the post (A knotted rope tied to a convenient ring near by answers well for this hand hold)

Procedure General Instructions —The individual to be tested is referred to as the subject The persons giving the test are first the adjustor second the operator

The duties of the adjustor are to place the loop in the assigned position about the arm or leg support it there with one hand and if necessary the arm or leg of the subject with the other He gives the command hold back to mark the beginning of the pull and stop to mark the end

The operator has the handle of the balance in his right hand and the body of the balance in his left

After the loop is adjusted the adjustor gives the command hold back At this command the subject contracts with all his power the muscle group being tested and simultaneously the operator pulls upon the spring balance Tension must be developed as rapidly as possible without jerking and must be increased until the resistance of the subject is actually overcome At the command stop the pull is discontinued immediately The scale is read at once and the reading recorded by the assisting clerk The sliding indicator of the scale must always be returned to the zero position immediately

Tests are taken with the subject fully dressed

Muscle groups that are reported by the subject to be sore are not tested

Calculation of Total Strength—The sum of the strengths shown by the individual muscles included in the short test constitutes fifteen per cent of the entire strength as found by the complete test (see Table 8) To calculate the entire strength therefore the sum of these determined strengths must be multiplied by the reciprocal of 0 15 which is 6 67 The product thus obtained is the figure for the strength of the subject If for any reason any muscle group was omitted from the test assume the strength of the omitted muscle to be the same as that of the corresponding muscle on the other side

"*Detailed Technique of the Tests a Pectorals*—The subject stands at attention with the middle of his back pressed firmly against the upright post and the hand of the arm not being tested grasping the hand hold The arm to be tested is allowed to be limp in the hands of the adjustor until the command hold back with which command the pectoral muscles are contracted as strongly as possible The adjustor stands directly in front of the subject facing him places the loop of the balance about the arm to be tested just above the elbow with one hand he holds the loop in position and grasps lightly the subject s hand or wrist with his other hand Keeping the subject s arm straight the adjustor draws it across the subject s body as far as possible keeping it as close to the body as can be done and still give clearance for the loop At the command hold back the subject s effort is to hold the arm from being drawn backward and downward from this position The operator standing at the subject s side holds the balance in a line downward and backward from the subject s elbow in such a position that the arm as drawn back will just clear the subject s body At the command hold back the operator develops sufficient tension to draw the arm down to the side of the body The command stop must be given and the pulling discontinued before the arm has been drawn beyond the vertical line

"*b Forearm Flexors*.—The subject lies on his back on the table with his heels pressed firmly against the cleat The adjustor stands at the subject's left for both flexors His right hand holds the subject's elbow to the table his left hand brings the subject's forearm into a position of flexion about fifteen degrees toward the shoulder from the vertical and adjusts the loop about the wrist so that its upper edge is at the crease in the skin at the base of the hand The operator stands at the foot of the table he develops tension at the word of command The command stop should be given when the forearm reaches the vertical

"*c Thigh Adductors*.—Position of the subject same as in the above test except that he presses against the cleat only with the foot of the leg that is not to be tested He may steady himself by grasping the edge of the table The adjustor stands at the foot of the table with one hand he places the loop in the hollow just above the malleolus (an equally correct index is to have the loop just clear of the top of an ordinary man's shoe) he seizes the subject's heel with the other hand lifts the leg until the heel is just high enough to clear the other toe and then draws the leg into extreme adduction The toe of the leg to be tested must be kept vertical The operator stands at the side of the table and develops tension at the word of command The command stop should be given as soon as the leg is drawn into line with the axis of the body

d Thigh Abductors.—The position of the subject and of the adjustor is the same as in the above test The loop is placed as for the adductors except that the direction of pull is opposite The leg to be tested is drawn out fifteen degrees beyond the line of the body the effort of the subject at the command hold back is to prevent the operator from drawing the leg into line with the body The command stop is given just as the leg reaches the midline

The most convenient order for the tests is as follows

Right pectoral
Left pectoral
Right forearm flexor
Left forearm flexor
Right thigh adductor
Left thigh abductor
Right thigh abductor
Left thigh adductor

"Although the satisfactory giving of the test requires careful training and considerable practice on the part of operator and adjustor the demand upon the subject are not great We have made successful tests upon subjects with a very limited knowledge of English and only ordinary intelligence Much time can be saved by letting subjects not yet tested see the

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Detailed Technique of the Tests a Pectorals —The subject stands at attention with the middle of his back pressed firmly against the upright post and the hand of the arm not being tested grasping the hand hold The arm to be tested is allowed to be limp in the hands of the adjustor until the command hold back with which command the pectoral muscles are contracted as strongly as possible The adjustor stands directly in front of the subject facing him places the loop of the balance about the arm to be tested just above the elbow with one hand he holds the loop in position and grasps lightly the subject s hand or wrist with his other hand Keeping the subject s arm straight the adjustor draws it across the subject s body as far as possible keeping it as close to the body as can be done and still give clearance for the loop At the command hold back the subject s effort is to hold the arm from being drawn backward and downward from this position The operator standing at the subject s side holds the balance in a line downward and backward from the subject s elbow in such a position that the arm as drawn back will just clear the subject s body At the command hold back the operator develops sufficient tension to draw the arm down to the side of the body The command stop must be given and the pulling discontinued before the arm has been drawn beyond the vertical line

ranged from nineteen to thirty-seven, averaging twenty-six and six-tenths. The significance of this figure seems as follows. If two individuals of equal weight differ widely in strength, four factors may be responsible. The first of these is actual amount of muscle; the second, the bodily configuration of the individual. In this latter instance Martin and Rich found one-half of their strong subjects among the tall and one-half among the short, with the average strength of short and tall men about equal.

The third and fourth factors, muscle quality and innervation, are unknown but are probably of great importance. As has been pointed out elsewhere in this article, individuals vary in the manner in which they fatigue and we have evidence to justify locating this difference peripherally. At the same time and in the absence of definite physiological evidence we are unable to neglect the central nervous possibilities which may establish such differences. Martin and Rich believe that the strength-weight ratio is an important index of muscle quality and innervation and suggest dividing individuals into the following five classes:

Class	Strength-weight ratio
A	more than 30
B	25.1 – 30
C	20.1 – 25
D	16.1 – 20
E	less than 16.1

In a series of 122 individuals classified in this way, the following division occurred:

A	14 per cent	Exceptionally strong
B	46 per cent	More than average strength
C	38 per cent	Men of average strength
D	2 per cent	Men of less than average strength
E	0 per cent	Weakling

These figures were obtained from study of students in fine physical condition. In the case of clerks and factory hands the proportion of C and D men would be higher. Finally Martin and Rich remark:

This classification based on the strength-weight ratio draws no distinction between small men of good quality and large men of equally good quality, although the latter will obviously be actually much more powerful than the former. For the practical purpose of assigning men to categories in accordance with their ability to achieve it would appear that some modification of the classification might well be made in which there is recognition of the importance of absolute muscular power as well as of good muscle quality and good innervation. This end would be achieved if definite lower limits of strength were assigned to each class. Tentatively we would suggest the following limits: class A, 5,000 pounds; class B, 4,000 pounds;

test carried out on others In this way they learn what is expected of them and carry out their part promptly when their turn comes A few seconds over one minute is usually enough time for carrying out a short test"*

Using this method, Martin and Rich give the normals shown in Table 8

TABLE 8

Muscle Group	Adult Males	13 to 18 Years
Feet		
Plantar flexion	10 00	9 30
Dorsal flexion	2 85	3 20
Inversion	1 90	10
Eversion	1 60	2 00
Thighs		
Adduction	1 50	1 55
Abduction	1 40	1 50
Extension	3 70	3 00
Flexion	3 20	3 10
Knees		
Extension	3 30	3 30
Flexion	1 75	1 70
Shoulders		
Pectoralis	2 35	2 10
Latissimus dorsi	1 70	1 45
Anterior deltoid	2 10	2 00
Posterior deltoid	1 40	1 50
Forearms		
Extension	1 50	1 60
Flexion	2 25	2 50
Wrists		
Extension	1 05	1 35
Flexion	1 35	1 90
Fingers		
Extension	0 65	0 70
Flexion	2 95	2 75
Thumbs		
Adduction	1 30	40

AVERAGE PERCENTAGE DISTRIBUTION OF STRENGTH AMONG THE MUSCLE ADULT MALE FOR COMPARISON THE DISTRIBUTION FOR CHILDREN OF 13 TO 18 YEARS IS GIVEN ALSO

A further point of interest is found in the relation of strength to weight In Stanford students under intensive military training the weights averaged 146 6 pounds and the strength 3 900 The ratios of strength to weight

* A very satisfactory spring balance and scale is furnished by John Chatillon and Sons 85 to 93 Cliff Street New York City as Special Strength Tester Style No 100 B The capacity should be designated in ordering and can be had in pounds (200) or kilogram (100)

King[38] has published the only extended statement relative to this test having employed it in studies of soldiers suffering from "irritable heart," the "effort syndrome" group of Lewis[17] and gives the following directions for its application

"The test is performed in a darkened room The subject exposes the interior surface of the forearm against which the concentrated rays of the 25 W Mazda bulb are directed A black background is very helpful in resting the observer's eyes and in increasing the definition of the area to be observed The Ryan instrument is grasped and the wooden marking disk is pressed on the subject's forearm until the standard pressure (90 gm) is indicated Then two strokes are made without changing the pressure across the forearm as rapidly as feasible A stop watch is snapped at the end of the first stroke At from ten to thirty seconds white lines appear where the strokes were made The watch is snapped read and restarted with the loss of only a fraction of a second The first reading indicates the latent period As soon as the first indication of blushing of the white lines sets in the watch is again snapped this second reading is the duration time and it is according to Ryan the more variable and significant figure"

Ryan and Cordon in tests made upon nurses and a few other individuals whose work is not specified found the "duration time" always decreased with fatigue and increased with rest sleep etc King found the test valuable in his group study of cases of irritable heart but unfortunately the figures he gives for these constitutionally inferior individuals are not coupled with satisfactory normals The test has the advantage offered by that of Martin of being perfectly objective It has the disadvantage of a somewhat inexact end point together with the impossibility of employment in individuals with swarthy skins

Psychophysiological Tests

All such tests have as their object the procuring of some simple measurement of fatigue to be applied before and after carrying out a day's work The measurement itself does not center upon the muscles most actively in use in the task but utilize another function to indicate the general manner in which the individual is keeping pace through repair with the energy expended in his task Tests of visual acuity auditory acuity complex reaction time etc have been employed but none of them have produced results worthy of comment[39] The laboratory has as yet failed to evolve tests of the above types which are sufficiently impersonal and simple to be employed in the estimation of fatigue in the average factory employee

class C 3 000 pounds class D 1 600 pounds The practical effect of these absolute limits would be to require small men to show higher strength weight ratios than large men if they are to be placed in the higher classes In no case would we reduce the limits suggested for the strength weight ratios of the different classes It would follow that a man weighing distinctly more than the average would have to show a strength well above the lower absolute limit of any given class in order to attain a strength weight ratio that would admit him to it "

We agree with Spaeth[33] in believing that this simple and very objective test has an important future not only for the initial placement of workers in tasks fitted to their strength but also in the estimation of fatigue Unfortunately there is little published data as yet in relation to the industrial utility of the test Martin[34] in a very brief note remarks In industrial operations calling for the exercise of strength there is a pronounced tendency toward a standard strength for each job In other words operation in which a definite exertion is required tend to develop a degree of strength determined rather by the exertion than by the weight of the worker

Comparisons of strength at the beginning and end of the work shift showed that in general there is in the easy jobs a tendency to make a better showing at the end than at the beginning In the operations requiring moderate exertion the stronger workers do better at the end than at the beginning but the weaker workers are likely not to do so well at the end as at the beginning In the hard jobs all the workers tend to do less well at the end than at the beginning

"Comparison of the daily strength records of workers with their daily production records shows that on days in which good strength record are made production is likely also to be good and on days in which poor strength records are made output is likely to be poor'

Ryan s Test [1]

Ryan and Gordon have endeavored to make use of a vasomotor reflex originally commented upon by Marey[16] Langet[37] described this reflex a follows By stroking the skin with a blunt instrument one sees first a white line from mechanical stripping then twenty or thirty seconds later the white persistent line appears This line differs from that made with a sharp instrument which has a red center and white edges " Ryan and Gordon[35] devised an instrument with which one may make a stroke under uniform conditions of pressure This instrument has had extensive use by the American Committee on Industrial Fatigue of which Ryan was a member but as in the case of Martin s test the real facts as to its utility are not available

SCHEDULE OF INDUSTRIAL CONDITIONS WITH REFERENCE TO DETERMINATION OF WORKING CAPACITY
(Slightly modified from Florence[40])

I Length and Intensity of Activity
II Nature of Work
  Type of study available for estimation of fatigue
    A Statistics output
    B Accident incidence
    C Power utilization
    D Sickness and out time medical supervision
    F Objective tests
III Type of Workers
    A Sex age and race
    B Experience Date of entering industry Former occupations
    C Habits and home conditions
        (1) The amount and use of earnings Thrift
            Food Diet and time of meals Alcohol
            Sleep and recreation Home accommodation and hygiene Support of dependents
        (2) Method and length of transit from home to work
        (3) Duties outside factory (house work of women etc)
        (4) Sexual and family relations
    D Point of view Animus Trade unionism patriotism economic self interest herd instinct etc general intelligence
IV Factory Conditions
    A Physical time and place of work
        (1) Air temperature and humidity ventilation and room space dust and fumes exhaust systems smell
        (2) Light volume concentration glare
        (3) Noise volume irregularity vibration
        (4) Safety device and first aid
        (5) Feeding
        (6) Drinking water rest rooms bathing facilities
    B Social and economic
        (1) Flow of work depressions and rush orders Routing
        (2) Creation of staff Appointment and dismissal Permanency of tenure
            Unemployment Instruction and supervision
        (3) Maintenance of production
            Incentives natural interest in work scale method and assurance of wage payment
            Discipline

During the war much interest was created by the use of psychophysiological methods for the selection of individuals suited to the strains of aviation In the case of such highly individualized and responsible tasks we may expect to see the development of psychophysiological tests but as yet it is safe to say that such tests cannot be included in any discussion of the practical methods of estimating fatigue Readers interested in this development of the subject will find discussions of apparatus method etc in the monograph from the Carnegie Nutrition Laboratory entitled Human Vitality and Efficiency under Prolonged Restricted Diet (Benedict F C Miles W R Roth P and Smith H M Publication No 280 of the Carnegie Institution of Washington 1919) and in the Manual of Medical Research Laboratory (War Department, Air Service, Division of Military Aeronautics Washington D C, 1918)

Output

The recent war has given enormous impetus to efforts to gauge fatigue in terms of output If the observer wishes to employ this method it has become increasingly evident that he must be very cautious in a number of directions

a It must be kept in mind that the eventual object is to gain information as to the sustained working capacity of the individual In order to do this periods of observation must be long and every care must be taken to exclude as causes of diminishing or increasing output factors outside the actual task under observation

b The task studied must be sensitive to this type of observation It is both misleading and a waste of time to study processes in terms of output where the rhythm of the machine determines the amount of work accomplished

c The observer should constantly ask himself whether output data are really registering the physical condition of the worker Reduction in output does not necessarily mean that a worker s task has caused actual physical impairment since it may have brought about avoidance of this very thing Therefore while a diminishing output in well selected tasks is always of great economic interest it is not necessarily of medical importance unless correlative observations can show an accompaniment of actual or imminent physical or mental damage

Florence[40] has taken the lead in the recent observations upon output in relation to fatigue and gives the following schedule for the guidance of the *investigator* in this field Its comprehensiveness is perhaps the best warning which can be offered against the indiscriminate use of badly gathered data

ing owner of the Zeiss Optical Works. In 1891 the hours of work in this factory had reached nine per day and they were held at this figure until 1900. During this nine-year period, owing to very accurate methods of accounting and to the fact that the men were universally on piece work, figures for wages were accumulated which indexed very accurately the amount of work accomplished. In 1901, after this long control period and using of course the same operatives, Abbe reduced the working day to eight hours purely as an experiment, with the results indicated in Table 9.

This table shows that the men in Abbe's employ earned more money in the eight than in the nine-hour day and they thus must have accomplished more work. Had their hourly earnings failed to increase in the ratio of 8 : 9 or 100 : 112.5 the experiment from Abbe's point of view would have been a failure. As a matter of fact, with the exception of one rather small group of microscope grinders doing very fine hand work, the ratio of increase is invariably above 100 : 112.5. One may thus argue that these workmen, when permitted more leisure, gradually experienced a degree of physical betterment which enabled them quite insensibly to carry on their tasks at such an increase of speed that the hour a day which had been lost was more than made up. It is significant that in the case of Abbe's workmen the reduction in hours was not desired and that the resulting increase in money earned was quite unexpected.

During the war certain English statistics of similar type became available. Table 10, taken from the English reports[4], is instructive.

The women observed were engaged in moderately heavy labor and were experienced workers so that practice had nothing to do with the output increase. Vernon[4] remarks:

The output data of Table 1 [the table quoted, table 8] indicate that the beneficial effect on output of a reduction in the weekly hours of labour from 74.3 to 67.5 was not immediately manifest. Even a reduction to 52 hours seemed to have no influence, but this was owing to a temporary shortage of material. From February 27 onwards the hours of labour were 66½ per week (or 58½ in the second week of each month, when there was no Sunday labour) and we see that during a period of eight weeks the hourly output now averaged 23 per cent. more than in the pre-Christmas period. The total output is 17,343 per week, or 8 per cent. more than in the pre-Christmas period, in spite of the hours of labour being nominally 10.5 less and actually 8.5 less. It is probable that the 60 hours worked per week were still too many to give the best total output, but at least they justify the statement that in order to maintain a maximum output women engaged in moderately heavy manual labour should not work for more than sixty hours per week. Observations adduced below suggest

It is evident that in the study of industrial fatigue, if one employs such a schedule as the above he must first analyze the task and then center upon the gathering of statistics in the field which is apparently most apt to provide useful information Thus in one shop power utilization might be chosen in another sickness and out time, but in every case this major interest should be controlled by as much allied data as can be secured

TABLE 9

Occupation	No of Persons	Average Age	Average Length Service Years	Earnings Per Hour in Pf		Ratio of Increase
				9 Hour Day	8 Hour Day	
Optical Operations						
1 Lense setters fine hand work	[illegible]1	31 1	12 7	7 8	84 9	100 116 6
2 Microscope grinders etc	[illegible]0	33 2	13 8	79 1	86 5	100 109 4
3 Other hand grinders and centerers entirely hand work	59	26 1	7 5	60 4	70 5	100 116 7
4 Machine grinders entirely machine work	19	32 1	5 8	52 2	6 0	100 118 8
Mechanical and Auxiliary Work						
5 Adjusting rooms entirely hand work	[illegible]2	31 7	8 2	65 5	76 7	100 11[illegible]
6 Mounting rooms chiefly hand work	[illegible]0	3[illegible] 9	11 6	[illegible]6	78 5	100 117 9
7 Turning and milling entirely machine work	23	35	11 1	57 6	68 0	100 118 1
8 Polishers and lacquerers entirely hand work	17	34 7	11 2	53 8	63 3	100 117 7
9 Engraving entirely hand work	5	27 2	6 8	56 1	66 9	100 119 3
10 Molders entirely hand work	6	3[illegible] 2	9 7	5[illegible] 4	[illegible]4 8	100 114 9
11 Carpenters part hand part machine	15	35 2	10 5	5 3	6 9	100 120 3
1[illegible] Case maker chiefly hand work	6	30 4	6 4	55 7	6 8	100 11 7
	33	31 6	9 6	61 9	[illegible]1 9	100 116 2

INCREASE IN EFFICIENCY OF THE 233 WORKERS —CLASSIFIED BY OCCUPATION

If now we suppose and we have no guarantee that our supposition is correct that all the conditions of Florence's schedule have been reasonably well fulfilled what sort of actual field results can be presented? Goldmark[41] presents from the work of Abbe the first really significant data we have available and these data have not been surpassed either in character or in exactness by any other work In 1888 Ernest Abbe became the manag

that an equally good total output could be maintained if the actual working hours were reduced to 56 or less per week

It is noteworthy that in this instance as well as in that of Abbé the increase in efficiency came slowly the women assuming a new and more rapid rhythm of work after a definite period of time This delay would seem to represent the period necessary for them to acquire the physical and nervous well being expressed in their final enlargement of output

Another instance of somewhat similar type but turning out differently is pictured in Table 11 taken from the same report[42]

TABLE 11

Statistical Period	Average Hours of Actual Work	Average Hours of Broken Time	Average (Relative) Hourly Output	Hours x Output
Five weeks preceding Christmas (November 15–December 19)	75 6	2 9	100	[illegible] 560
Two weeks at Christmas	50 0	2 7	106	
Six weeks after Christmas (January 3–February 13)	0 9	4 6	106	7 515
Eight weeks later (February 1–April 16)	59 4	4 4	108	6 415
Two weeks at Easter (April 17–April 30)	40 8	4 6	95	

17 YOUTHS BORING TOP CAPS

In this instance one of two things may be true either the youths in question were not pushed to the peak of capacity in the first period or the work was so far et by the machine as to be insusceptible of study from this point of view

Spaeth[33] has pointed out one of the great defects in the statistical method namely that when it is successful in disclosing damage as a result of excessive hours or unsuitable work it does so after a large amount of harm has been done It is in no sense preventive and in the case of fatigue as in other branches of industrial hygiene even a small amount of prevention outweighs all else

Finally it should be clearly understood that neither the physiologist nor the physician should look upon any of the output data as expressing a brief for a uniform eight hour day or for a day of fixed length of any sort It is manifest that from the medical point of view the length of the working day should differ markedly in different tasks and should be determined by the character of the work It is however improbable that data relative to physical efficiency will ever play much of a part in the future regulation of working hours A multitude of other considerations have taken charge of this question and it is probable that the usefulness of data collected by an industrial physician in his own plant will be confined very strictly to

TABLE 10

Week Ending	Actual Hours of Work Per Week		Nominal Hours of Work Per Week	Hours of Broken Time Per Week		Relative Output Per Working Hour		Hours of Work × Relative Output	Remarks Concerning Output
Nov 14	62.0		67.5	5.5		98			Hourly output fairly steady
Nov 21	68.8		75.5	6.7		99			
Nov 28	66.7	68.2	75.0	8.3	6.6	10[illegible]	100	6,820	
Dec 5	[illegible]0.9		77.2	6.3		96			
Dec 12	69.1		76.2	7.1		99			Typical rise in hourly output before holiday
Dec 19	71.8		77.3	5.5		107			
Dec 26	41.8		46.0	4.2		105			Great fall in hourly output immediately after holiday
Jan 2	32.8					89			Subsequent considerable increase of hourly output whilst total output rises to a maximum 12 per cent greater than that of pre-Christmas period
Jan 9	65.2		69.3	4.1		113			
Jan 16	70.3	68.[illegible]	77.2	6.9	5.[illegible]	107	111	7,615	
Jan 23	70.3		76.3	6.0		112			Reduction of hours of labor from 74.3 to 67.5 has no immediate effect on hourly output, hence a considerable reduction of total output
Jan 30	62.4	61.6	68.5	6.1	5.9	111	107	[illegible],591	
Feb 6	60.8		66.5	5.7		102			Temporary shortage of material and reduction in hours of labor
Feb 13	49.2	48.4	52.0	2.8	3.6	108			
Feb 20	47.6		52.0	4.4		106			
Feb 27	61.4		66.5	5.1		118			
Mar 5	62.[illegible]		66.5	4.3		125			Effect of shorter hours of labor now established, and hourly output reaches a maximum. Total output 8 per cent greater than in pre-Christmas period
Mar 12	54.8		58.5	3.7		127		7,343	
Mar 19	62.1		66.5	4.4	4.6	121	123		
Mar 26	60.4	59.7	66.5	6.1		121			
Apr 2	58.6		64.8	6.[illegible]		121			
Apr 9	54.9		58.5	3.6		121			Typical rise in hourly output before holiday (Easter)
Apr 16	62.9		[illegible]5	3.6		1[illegible]6			
Apr 23	47.0		49.5	[illegible].5		125			

100 WOMEN TURNING FUZE BODIES

sleepiness and mounting toward disaster through days of trying work. This is the general effect which it seems possible to gain from over indulgence in any type of work. Spaeth speaks of this harmful development as "industrial psychoneurosis." To us it would seem that no new term is needed. All we need is conviction that any simple neuromuscular operation if carried to excess produces general as well as local effects, that the general effects depend on the condition of the individual at the moment and the amount of work undertaken. If the work is light and the subject in good health, recovery will be prompt and complete, but if the reverse is true disaster will result.

While the physiological organization of the neuromuscular apparatus is such as to guard against over use, the protection afforded is not complete and the individual frequently passes the limits of his restorative powers. We know far less about the possibilities and the time required for complete restoration to normal after the simplest tasks than we do about our actual ability to perform them, and in the opinion of the authors the most useful advances in the study of fatigue which coming years should show will arise through observations upon physiological repair made both in the laboratory and in the practical field of industry.

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that organization or neglected entirely as it clashes with what are apparently more vital economic issues

Accidents, Lost Time and Sickness

Frequent efforts have been made to correlate accident incidence with fatigue the idea being that the incoordination accompanying fatigue must account for some of the tremendous accident incidence which American industry shows But there is apparently no reliable connection of this sort Inexperience lighting and a thousand other factors so far influence accident incidence as to thoroughly becloud any effort at relating accidents and the diminishing physical efficiency of fatigue Lost time and sickness fall in the same category and in connection with them the industrial physician will have one of his greatest opportunities to contribute to medical science Recent figures indicate that the American workman loses six to seven days per year as a result of what is at present recorded as disability When the industries can come forward with accurately kept records upon disability classifying causes so that we may know what to attribute to fatigue a great step will have been taken Recent publications of the National Industrial Conference Board form excellent testimony as to our lack of knowledge upon this point In successive reports upon hours of work and health of cotton woolen and silk workers a certain amount of data is given as to the immediate effects of shortened hours upon output but because of complete lack of knowledge as to time lost from ill health prior to making the change in hours of work, no facts can be presented as to this most interesting and important phase of the problem You will find' writes Sir James Paget that fatigue has a larger share in the promotion or transmission of disease than any other single causal condition you can name' In spite of such an opinion and its endorsement by many authorities, no facts are available which really indicate the truth

Conclusion

The essential economic interest in fatigue as Spaeth[33] has brought out lies not with the normal process but with something intangible and cumulative which eventually makes itself felt in diminished efficiency and perhaps breakdown We do not expect do not wish to finish a day's work without fatigue We often speak of being 'healthily tired out" and look forward to the dreamless sleep which we are confident will follow At the same time there are few of us who are not cognizant of another experience one developing more slowly lacking perhaps the induction of

CHAPTER XXIII

INDUSTRIAL MEDICINE

By W. IRVING CLARK

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instituted physical examinations of all employees at Norton Co Worcester Mass At almost the same time numerous factories in different parts of the country began examining their workers and advising them in caring for conditions found at such examinations It is noteworthy that a number of doctors having little knowledge of similar work being done elsewhere all saw the need at practically the same time By their earnest and thorough work they were able to convince the industry for which they were working that the physical examination of employees from the highest executive down was an economically sound policy

In 1914 the Conference Board of Physicians in Industrial Practice was instituted under the secretaryship of Magnus Alexander there being then a large number of industries in the East with well equipped medical departments This Conference Board besides standardizing a first aid equipment and rules for the use of laymen in factories brought in contact with each other the medical heads of many important factories and developed many new ideas along both administrative and practical lines

In August 1917, the Conference Board published a report compiled by Mr Alexander on the Cost of Health Supervision in Industry in which ninety nine plants averaging from 140 to , 000 employees were analyzed upon a medical cost basis It is interesting to note that at this date there were easily accessible records of medical supervision in at least ninety nine plants and that the total number of employees thus supervised numbered 49, 544

In 1916 at Detroit 125 industrial physicians organized the American Association of Industrial Physicians and Surgeons The aims of the association have been to stimulate scientific investigation of the problems of industrial medicine to interest industries in the establishment of health departments and to raise the standards of physicians engaged in industrial practice The organization has increased in size steadily and now has approximately 1 700 members

The importance of industrial medicine in the eyes of the Government at Washington was evidenced by the establishment in 191 of the Division of Industrial Medicine and Hygiene in the United States Public Health Service under the direction of Dr J W Schereschewsky This division has increased in size and has cooperated with state departments of industrial hygiene of which there are now forty one In 193 the American College of Surgeons started a series of surveys on medical services in industry and has developed a set of minimum requirements which if met entitle the factory to a certificate In 1946 the College

HISTORICAL DEVELOPMENT

The health of workers in industry received surprisingly scant attention during the period of early expansion. Apparently neither employer nor state recognized the enormous economic factor entailed and except in a few isolated instances, little or no thought was given to what is today becoming one of the most important factors in economics. One reason for this was the rapid development of business with the almost limitless amount of labor pouring in yearly from Europe. Moreover the wastage of "hiring and firing" was not recognized, and a large labor turnover was considered a normal and unavoidable condition. In many factories and especially in mining camps a doctor was employed full time, but his function was almost entirely to care for accidents, the work was considered unscientific and not particularly desirable. The passage of workmen's compensation acts by state after state however induced employers to consider the safety of their workers more carefully than formerly and in case of accident to provide the most effective treatment possible.

The importance of the question of health to the country as a whole was shown by a federal investigation of 2,400 workmen's families in 1901. This brought out that 11.2 per cent of the heads of the families were idle during the year solely on account of sickness for an average period of 7.71 weeks or an average of about five days.

In 1909 public sentiment and activity was, for the first time, aroused vigorously to combat tuberculosis. A wave of publicity swept the country stimulating thought and effort toward prevention and cure. One of the most active participants in this movement was the Committee on Factories of the Chicago Tuberculosis Institute, composed of Drs James Britton, Theodore Sachs and Henry Faville, who introduced the idea of physical examination of workers in factories. Prior to this in 1906, Dr Frank T. Fulton had examined a number of workers in one of the large saw factories of Providence in an effort to isolate tuberculous workmen. Shortly after this Dr Harry L. Mock made a series of examinations for Sears Roebuck Co., Chicago, Ill., and the writer

instituted physical examinations of all employees at Norton Co Worcester Mass At almost the same time numerous factories in different parts of the country began examining their workers and advising them in caring for conditions found at such examinations It is noteworthy that a number of doctors having little knowledge of similar work being done elsewhere all saw the need at practically the same time By their earnest and thorough work they were able to convince the industry for which they were working that the physical examination of employees from the highest executive down was an economically sound policy

In 1914 the Conference Board of Physicians in Industrial Practice was instituted under the secretaryship of Magnus Alexander there being then a large number of industries in the East with well equipped medical departments This Conference Board besides standardizing a first aid equipment and rules for the use of laymen in factories brought in contact with each other the medical heads of many important factories and developed many new ideas along both administrative and practical lines

In August 1917, the Conference Board published a report compiled by Mr Alexander on the Cost of Health Supervision in Industry in which ninety nine plants averaging from 140 to [illegible]5 000 employees were analyzed upon a medical cost basis It is interesting to note that at this date there were easily accessible records of medical supervision in at least ninety nine plants and that the total number of employees thus supervised numbered 495 544

In 1916 at Detroit 1[illegible]5 industrial physicians organized the American Association of Industrial Physicians and Surgeons The aims of the association have been to stimulate scientific investigation of the problems of industrial medicine to interest industries in the establishment of health departments and to raise the standards of physicians engaged in industrial practice The organization has increased in size steadily and now has approximately 1 700 members

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issued a digest of industrial medicine and surgery based upon the surveys just mentioned[1] In 1935 the Air Hygiene Foundation, to become later The Industrial Hygiene Foundation of America, was started in Pittsburgh In 1937 the American Medical Association established the Council on Industrial Health The Council has influenced the establishment of committees on industrial medicine in State Medical Societies

Thus has developed what is called by some a branch of public health work by others a specialty in the medical profession, *Industrial Medicine*

It is a specialty in which only a certain type of doctor with special training is fitted to practice, and this has become so well recognized that a number of medical schools offer full courses while others give a short intensive series of lectures on the subject

With this brief historical sketch let us examine the subject in detail

INDUSTRIAL MEDICINE

Industrial Medicine is the application of the practice of medicine and surgery to the needs of the industrial worker The United States is an industrialized country employing about 16 million workers in industry The care of the health of these workers is of importance not only to the individual factory or mine but to the country at large Because of the segregation of workers into groups working together the importance of environment is evident, and the industrial physician assumes a public health function as well as that of a physician and surgeon

A complete medical service in industry comprises three fields of effort, industrial medical and surgical practice, industrial hygiene and industrial toxicology Industrial medical and surgical practice studies the prevention of accident and disease among workers diagnoses disease and both diagnoses and treats industrial accidents Its chief function is medical supervision of the employees Industrial hygiene studies and endeavors to control those general factors of the worker's environment which are unfavorable to health, it may be defined as "that branch of the medical engineering chemical and nursing sciences which is concerned with the study of the effects of environmental conditions in industry upon the health of industrial workers from the point of view of the incidence, the causes and the nature of the effects and the means of eliminating or minimizing the causes and thus removing or modifying the effects" (McConnell, W J, Metropolitan Life Insurance Co, New York) Industrial toxicology studies endeavors to prevent and in some cases treats

cases of poisoning occurring among workers exposed to toxic products in manufacturing These three functions are the work of the industrial medical department Anything which is not included does not belong to industrial medicine

From this it will be seen that a factory is really a community of workers and that the industrial medical department has as its duty the preservation of health, the study of disease and the treatment of accident within its boundaries While short excursions into the wilderness beyond are occasionally necessary these are merely exceptions which prove the rule that industrial medicine is practiced in the factory among its workers and only in the factory Thus there is a definite line drawn between the factory community and the general community outside the factory walls When as is sometimes the case the factory like the old feudal castle dominates the community and through its industrial medical department provides full medical care not only for the employees at their homes but occasionally for their families as well, it is not providing industrial but community medicine

Having outlined what industrial medicine comprises one must consider the position which the industrial medical department assumes in the organization of a manufacturing plant

The organization of the modern factory is extremely complex and differs in different companies However it may be simplified generally into four great divisions administrative and finance production sales and personnel The first division has to do with the development management and finances of the company as a whole the second division has to do with the production of the goods manufactured the third has to do with the distribution and sales of these goods the fourth deals entirely with the personnel of the organization

The personnel division usually is administered by a Personnel Director who is responsible to the General Manager or President of the company In some cases the Personnel Director is a vice president of the company in others the employment manager and in still others an industrial physician In some factories the industrial physician comes directly under the general manager and this method of organization is excellent for professional reasons as it requires a broad view to understand the importance of maintaining factory health If the doctor s work and department are looked upon as a necessary evil an overhead expense and a liability rather than as an asset half the value of a medical department to the company is lost for expansion and thorough work are vital to success

There are, from the point of view of the industrial physician, three types of factories, first, those employing over three thousand workers second, those employing between one and three thousand workers, third, those employing less than a thousand workers

The organization of the medical department in the first type is quite complicated because of its size and the large number of doctors and assistants employed That of the third type is extremely simple We shall discuss first the organization of the second type, later the third

Organization for Factory Employing 1,000 to 3,000 Workers

The department may for convenience be divided into three sections (Fig 1), each controlled by the chief physician These sections consist of the medical, sanitation, and visiting nursing sections Each section is a separate division and separately managed

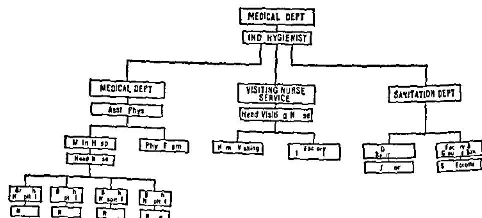


Fig 1 Chart of organization of a Medical Department in a factory of about 3,000 employees

The medical section deals with the preservation of the health of the worker and the treatment of accident and sickness

The sanitation section provides and maintains the highest type of sanitation in the factory, cooperating in this with the Engineer of the Plant

The visiting nursing section calls at the house of the worker and helps with his home problems especially in cases of sickness

The medical section is controlled by the chief physician and the work

is done by him and his assistants Whether he has one or more doctor assistants, depends upon whether the assistant works on a part or a full time basis The chief physician himself may work part or full time

There has been a great deal of discussion as to the relative advantage of part or full time doctors and no final decision has been reached as yet The full time doctor gives his entire time to the factory and does no outside work whatever The part time doctor in the type of organization we are now considering gives three or four hours of his time daily and has his private and hospital practice as well

In outlying districts and large factories a full time doctor is necessary but for the factory in the city the part time doctor seems more satisfactory A single doctor working full time does not have the variety of experience the strength and the ability to work possessed by three part time doctors each spending three hours daily at the factory The part time method is slightly more expensive but it enables the factory to procure doctors who otherwise would be unavailable

The number of factory nurses required will depend upon the number of workers and the plan of the factory Thus a compact type of factory consisting of one or two closely grouped plants can carry on its work with a single dispensary centrally located and only require one or two full time nurses while a factory which has a number of plants spread over a large area will require a certain number of sub hospitals each with a nurse in charge In a large number of this type of factory the minor injuries are treated by trained laymen who are furnished with first aid jars or boxes but this method is not as satisfactory as the multiple sub hospital system A nurse will do better work than a layman and her judgment as to the cases which should be sent to the main hospital to see a doctor is far superior to that of the usual first aid man

The number of nurses needed may be estimated roughly as one for each thousand employees plus one nurse for the main hospital The number of visiting nurses depends upon the number of employees As a usual thing one nurse per 000 employees is sufficient during the summer two during the winter The work of the industrial nurse differs from that of the hospital or private duty nurse as will become evident later on

Hospital and Equipment

1 A hospital dispensary and sub dispensaries (Figs and 3)
An office for the chief surgeon

3. An emergency room connected with the main dispensary, where sick or severely injured cases can have privacy
4. Those pieces of apparatus and equipment needed to provide an adequate medical and surgical service

Dispensary Layout

The position of the main hospital dispensary in relation to other departments has been found to be important There is a group of factory activities which are closely related and whose offices and facilities should be in close proximity This group consists of the Employment Department the Safety Engineering Department and the department which has charge of all matters having to do with Workmen s Compensation

The Medical Department must be close to the Employment Department in order that applicants for employment may be examined promptly it should be near the Safety Engineering Department so that accidents may be reported at once and for the same reason be in close contact with the department which reports industrial accidents It should also be near the office of the Personnel Manager

In a large factory the main hospital dispensary is centrally placed so that it is accessible from all sides and not too far from the sub dispensaries if these are required because of the size of the factory A general rule, which most factories follow, is to locate dispensaries at points that can be reached by a workman in less than five minutes

Surgical Equipment—The equipment of the main dispensary is simple, but its arrangement is important The object is to provide for the needs of an injured worker with minimum delay

It has been found that treatment units are a satisfactory method of meeting the problem A unit consists of all the appliances, apparatus and dressings needed for each type of surgical work A unit is so arranged that the doctor or nurse can reach the part to be treated, the dressings and the instruments with the least possible lost motion For hand and finger injuries a high chair with a large arm and an adjacent table on which the needed instruments and dressings are laid out, has proved satisfactory The same idea of unit arrangement is applicable to a dark room for the treatment of eye injuries to suitable chairs and foot rests for leg injuries and to an equipped room for the treatment of severe injuries

In addition to the groups of units mentioned there must be an adequate number of sinks or basins with running hot and cold water These sinks can well be placed along the center of the dispensary to be reached easily from all sides Foot tubs and whirlpool baths are a great convenience The sterilizer for instruments and another for dressings should be located centrally so as to be easily reached An instrument cabinet completes the necessary surgical equipment



Fig The Main Hospital Dispensary at Norton Company showing the arrangement of units for treatment of hand and foot injuries This dispensary has been in use since 1916 It was established to care for a factory of about 3,000 workers During the war it gave service to three and a half times that number Note units for treatment of hands and feet Emergency room seen through open door

Medical Section—The medical section of the dispensary is so arranged that patients having minor complaints can be treated quickly and where those having a history suggesting a more serious condition may receive the same careful examination that they would have in the office of a private physician Thus there should be one room connected with the dispensary where examinations can be made and another where pa-

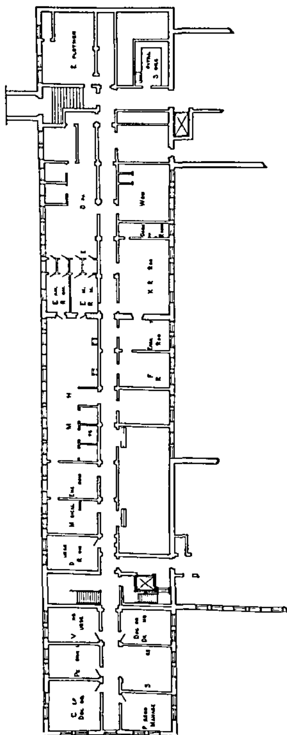


Fig. 5. Ground plan of Main Hospital Dispensary at Norton Company showing its connection with the Employment Department and the rooms for preplacement examinations

tients who require rest and observation may be temporarily given bed care

The treatment of minor sickness requires a small armamentarium of standard drugs thermometers etc which are immediately available A record room where records are kept under control of a filing clerk is adjacent so that the doctor may obtain the past history of any worker at a moment s notice

A factory dispensary frequently must be over manned with doctors and nurses in order to provide immediate care at all times The cost *to the factory of the dispensary staff is less than the cost of the time* which may be lost by workers awaiting treatment

The Industrial Physician

The personnel of the Medical Department consists of doctors and nurses as outlined but there are certain qualifications in both type and training which are important The chief physician must be a hospital graduate with surgical experience and a good general internist He must have organizing and executive ability and a general knowledge of public health problems He must be familiar with the methods of prevention of disease and accidents among the entire group of employees and be prepared to give constant supervision to their health, including a study of each individual the working conditions the hazards of each occupation the question of hours of labor and wages and adequate medical and surgical care of the sick and injured He must be trained also in the selection of occupations according to the physical qualifications of the individual and the restoration of the disabled to physical usefulness

The Industrial Nurse

The industrial nurse also should have special training She should be a woman of tact and have had experience in hospital accident rooms as well as some operating room experience The industrial nurse must use judgment more frequently than the nurse in private practice and the efficiency she shows in running her sub hospital or in doing her work in the main hospital is reflected in the number of cases applying for advice and treatment

The organization, therefore, consists of a chief physician on full time, with two or three assistant physicians on part time, of two nurses in the main hospital and one nurse in charge of each sub-hospital The sub hospitals should be visited by a physician every second day or when called by the nurse in charge

Besides the medical problems, which are controlled by the organization just mentioned, sanitation must be carefully arranged and supervised The chief physician should have under him a competent foreman who controls conditions of all locker rooms and toilets, besides caring for the cleanliness of the plant The foreman necessarily has under his supervision a large number of men who carry out his orders

The work of the Medical Department therefore, can be divided into supervision of health and supervision of sanitation in the factory Each will be considered in order

Supervision of Health in a Factory

The supervision of health consists in physical examinations of all workers and executives the examination of, and advice to all applying with sickness the care of all accidents the spreading of health publicity and the promotion of all things which go toward the making of a healthy working force The work may be summarized as being similar to that of the Medical Corps in the Army

Physical Examinations—The basic principle of good work is the scientific consideration of the physical condition of each member of the working force, and it is obvious that a physical examination at the earliest possible moment is the correct procedure It is now agreed among industrial physicians that the proper time for physical examination is while the worker is still an applicant and before he becomes a member of the working force The reason is the opportunity thus given to prevent contagious disease from being introduced into the factory and to advise proper placement of the worker

The routine adopted in most factories is as follows The applicant having been selected by the Employment Department for the work to which he is to be assigned, is passed on to the Medical Department for his physical examination He takes with him his physical examination blank on which the Employment Department has recorded the prospective employee s past working history This states the time and exact character of each previous occupation He is shown to one of the booths

indicated in Fig 3 and told to remove all his clothes to put a blanket around his shoulders and to wait The examining physician on duty is notified and steps from the hospital into the examining room unlocks the door and calls in the applicant The usual routine order is weight, height eyes ears nose, throat neck chest heart lungs abdomen inguinal region, genitals, back rectum upper extremity lower extremity reflexes blood pressure urinanalysis The first four of the above may be made by a male nurse, if one is employed thus saving a certain amount of the doctor s time The eye test is made with the Snellen card at ten or twenty feet While ten feet is not accurate it is sufficient indication of the applicant s vision to show whether a more careful examination is necessary The eyes are inspected carefully for corneal scars conjunctivitis or other abnormality

An inexpensive watch with a loud tick is used in the hearing test and the number of inches from the ear at which the watch can be heard gives a recordable figure If the watch can be heard at three feet the hearing from an industrial point of view, may be considered normal The canal is examined for impacted cerumen or evidence of otitis media

In examining the nose only gross defects such as deviation of the septum ulceration or occlusion of nostrils are noted Examination of the teeth is general but attention of the applicant should be called to the presence of teeth needing attention the care of the teeth and pyorrhea Examination of the throat is especially directed toward the discovery of secondary syphilis and possible sites of focal infection in the tonsils The examination of the neck is to determine especially signs of old or recent tuberculous adenitis and the presence of simple or exophthalmic goiter

The examination of the heart and lungs is performed in the usual manner It has been found advisible to exercise the applicant by having him hop fifty times on one foot in order to determine the cardiac action under slight fatigue as well as to bring out murmurs The blood pressure then is taken Men with marked cardiac lesions provided the compensation is not disturbed can work for years at manual labor if properly supervised The examination of the pulse before and after this exercise also is valuable

The abdominal examination is made with the patient in the recumbent position and special attention paid to the umbilical region and the right lower quadrant the former to eliminate umbilical hernia the latter for signs of chronic appendicitis

Examination of the inguinal regions is for adenitis and hernia To

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INDUSTRIAL HEALTH EXAMINATION

Empl y r C ty State
Name Add es Clock No
Ag f M t l St t s S S l S c N
P r al Phys c N xt f K n

Fe son l and Famil H t y
Immu zat R c d

O p t o al H t y

Phys al E mi at n D te E m r

H ght W e ght Che t M a u em nt {I p r t n / E p rat on}

T mpe at e Pulse {R t g / Aft E r} G rth

B d P essu e Po ture M sc l t e Nutr t n

Sk Glands H Scalp

V s {Di ta t {R ght / Left} / Ne {R ght / Left} / Col Sense} Correct d {R ght / L ft} C r ted {R ght / Left} D pth I e ept on Eyeg ou d

H a ing {R ght / Left} No Th at Tongue

T n ls N k

T eth G m

Lung {R ght / Left}

He t

Abd m H

Gen tal Re t m Pro tat

Sp ne

Jo ts R fle s H ds F t

Dy m h a

L b at y D ta D te E am n

Ur App e Sp fi Gr ty Suga Alb n S d m t

Blood H mogl b Sm S d mentat n R te

Wa se mann Kah Kl e

X Ray Ch st Oth

P so l ty D ta

Appe {N t / Car l / Sl e ly} T mp a e t {A gr / Q et / Cooper t / N re at} I t ll g e {O k / A ag / D t}

C mp at S hool g {Al a d / A e g / R t d} S y {H gh / Med m / Low}

S mm y a d R m d t R t g

C mpar t s hool g f s t th l l l edu at on atta n d in omp s with the l ld th f ly

Fig 4 Form recommended by The Council on Industrial Health American Medical Association for recording physical e amination

make this examination the inguinal canal should be palpated carefully and the applicant told to cough The external ring should then be explored with the tip of the index finger Pressure is exerted against the scrotum pushing the skin up and into the ring In this way the size of the ring is rapidly determined and the applicant instructed to cough Any mass in the canal thus is readily recognized

The examination of the genital organs is to exclude urethritis and primary syphilis and to note hydrocele or severe varicocele This part of the examination should be made in a quiet, matter of fact way and no questions as to the presence or absence of disease asked the applicant

The inspection of the back should be made with patient standing erect and any abnormality or curvature should be noted He is then asked to bend over and the action of the spine is noted The anus can be inspected at this time and a rectal examination made

Inspection of the extremities reveals amputations deformities, etc as well as varicosities and flat feet It is advisable to put the applicant through a set of simple motions which will immediately demonstrate a stiff or poorly functioning joint A specimen of urine is collected for later examination It is well as a routine procedure at some time during the examination to test the knee jerks Either prior to, or following the examination a chest x-ray is taken, and a specimen of blood is drawn for serological examination

Such a physical examination can be conduced with great rapidity after a little practice and usually is completed in from eight to ten minutes The results of the examination are entered upon an examination card and the man's classification is a physical risk entered upon the employment card (Fig 4)

Health Classification of Workers —This rating consists in classifying a man as an A B C or D risk

A Signifies a normal man
B The man has several slight defects
C The man has one or more serious defects and should be assigned to only certain types of work—consult with doctor
D The man is a bad industrial risk at any work—consult with doctor

The industrial physician should be thoroughly familiar with the general type of work done in each department of the factory When he finds an applicant with defects sufficiently severe to place him in the C or D rating he consults with the Employment Manager as to the exact

he is directed to a booth where he can undress in privacy He is then called into the examination room where he is examined by a doctor The results of the examination are entered on a physical examination card The doctor knows the type of work at which the applicant is to engage from the Employment Department card which accompanies the applicant to the examination room The doctor rates the applicant as an A B C or D risk If the risk is C or D he consults with the Employment Department in order that the worker may not be put at work for which he is not physically fitted C and D risks are entered on a separate sheet for reexamination in six months The Employment Department then enters the man as a workman in the factory

Reexaminations are made upon all workers who are transferred from one department to another first as a check on their general condition second in order to be sure that no man is transferred to work for which he is unfitted

Periodic Examinations—It is part of the routine of a well run industrial medical department to reexamine periodically all employees from the executives down through the working force

The object of these examinations is to prevent the development of disease by detecting it in an early stage The ideal plan is an annual examination but in large factories this is impractical The alternative is to plan for the annual examination of men who have defects found at the original examination of those who are working where there is an industrial hazard and of those who have undergone recent operations or who have had serious illness during the past year

These examinations are not made hurriedly but by appointment at a time when the doctor can do careful work and discuss his findings with the patient When a defect is found the patient is referred to his family physician for further examination and treatment

Such examinations are recorded and together with the examinations made at the time of hiring and following sickness operation or accident constitute an excellent running commentary on the worker's physical condition

Information obtained during these examinations is considered confidential as in private practice The objects of physical examination are

1 To place the worker at work for which he is physically fitted
2 To inform the worker of any defects found at examination and to cooperate with him in remedying these defects
3 To advise the worker as to a healthful method of life

work to which the applicant is to be assigned It is then decided whether the work is suitable or not for the applicant, and if not, whether there is work in any department needing workers which is suitable If such work is available, the worker is sent to the proper department, and the Employment Manager notifies the foreman of the department that the new worker should not be put at any but the work assigned without consulting the Medical Department If it is found there is no place where the applicant can work without danger to himself, his defect is explained to him the type of work which he may safely do is outlined, and he is advised of factories where work of the kind for which he is physically fitted can be obtained It is however, seldom necessary to reject if men are kept under medical supervision

Within the last few years an effort to place physically handicapped workers has developed beyond the more informal method outlined above In order to place a worker having defects, the physician must know not only the physical condition of the worker but also the physical requirements of the job and those environmental factors which may be of importance in his proper placement Each job may have specific requirements which must be evaluated against the physical condition found on examination in determining the worker's ability to do the job Thus a worker with an impaired knee joint would not be able to perform his work satisfactorily at a job which required climbing, kneeling or pulling heavy objects

The factor of environment includes exposure to heat, dust or chemical fumes

The information needed by the doctor is provided by a job requirement analysis This consists of a study of every job in the plant and a written analysis of the hazards as well as of the type of mentality and the physical ability needed by the worker who is assigned to the job With this list of jobs and their requirements before him, the industrial physician is able to decide whether or not the applicant is mentally and physically fitted to do the work designated and if not, at what job he should be tried The war has shown that workers with a variety of physical disabilities can do good productive work, if properly placed and instructed

The use of job analysis prevents dissatisfaction on the part of the new employee and provides the foreman with a worker who is physically and mentally competent to do the work given him[1]

To sum up the applicant for a position first presents himself to the Employment Department If he satisfies the Employment Department,

responsibility for the patient s reporting to the factory dispensary as soon as he is able

The cycle of treatment of any injury should be unbroken from the reception of the injury to the patient s return to work This cycle may

Slight Injuries



Fig 5

Injuries of Medium Severity

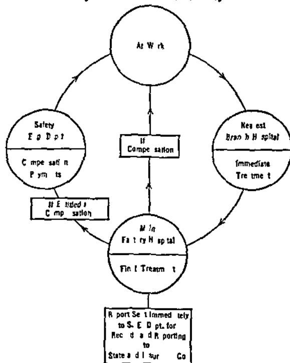


Fig 6

Fig 5 Accident cycle in slight injur es showing course of injured workman to and *from branch hospital*

Fig 6 Accident cycle in injuries of medium severity showing course of injured workman and points of contact with *Health and Safety Departments In this case the* workman is supposed to be in condition to report at Main Hospital for treatment

be diagrammatically shown as in Figs 5 6 and 7 If this method of supervision is carried out the injured worker receives more complete and systematic attention than can be obtained by any patient except under army control The advantage to the factory is the return of the worker after a minimum of lost time The advantage to the worker is the constant and thorough attention to his injury and the concentrated effort

4 To check the worker's physical condition periodically and to discuss with him any changes found

Care of Accidents

Considered from the legal point of view this is the most important work of the industrial physician, considered from the economic and practical point of view it is the least important, although most spectacular, part of his work It will be shown later that infinitely more time is lost because of sickness than because of accident The proper treatment of accidents may be divided into three parts, the immediate or first aid treatment, the intermediate or factory dispensary treatment, the hospital or final treatment These will be considered in order

The immediate or first aid treatment is carried out either by a layman in the department in which the accident occurs or by a trained graduate nurse in a sub hospital The treatment by laymen has been standardized by the Conference Board of Physicians in Industrial Practice and this standardization has stood the test of many years' experience[4]

The graduate nurse at a sub-dispensary has (more) equipment and is able to handle cases more effectively than a first aid layman In trivial injuries the patient is given his complete first treatment and any subsequent treatments which are necessary by the nurse or trained layman In moderate severe accidents a first dressing only is applied, and the patient is immediately transported by stretcher or automobile to the factory dispensary If the injury is severe, the doctor is called from the dispensary to the sub-hospital to point where the injury was received He administers the first treatment personally and arranges for the transportation of the patient After arrival at the factory dispensary the patient is examined carefully, and a record is made of all injuries found If a wound is present it is cleaned, and any necessary operation is performed Then the patient is sent home or to a general hospital This completes the intermediate treatment

In severe cases or those requiring major operative treatment the patient is sent to a general hospital where the final treatment is given After discharge from the hospital the patient is advised to report as soon as able to the factory dispensary for examination by the doctor The Visiting Nurse Service which is discussed later has for part of its duty the following up of such cases at the hospital and the home and also the

It has been emphasized by physicians, who do a large amount of accident work that the preservation of an aseptic wound depends more upon the care and thoroughness of the cleaning and dressing than upon the agent used In dressing injuries the most careful asepsis must be maintained as the tissues already partially devitalized by the trauma readily become infected The proper protection and immobilization of the injured part prevents infection produces confidence and promotes healing

A worker receiving a severe injury is given primary treatment at the main dispensary and is then transported to the nearest general hospital where his injury receives the required treatment

Dispensary Treatment—The following may act as a guide to standardizing the factory dispensary treatment of the more common types of injury

1 Wounds of all types
   a Clean throughly with soap and hot water using sterile gauze
   b Flush with sterile normal saline solution
   c Paint with antiseptic solution
   d Remove with scalpel and scissors all devitalized tissues
   e Suture with silkworm gut if suture is advisable
   f Apply sterile gauze dressing
   g Splint if wound is large
2 Fractures —simple
   a Make primary reduction at once when possible endeavoring to reduce deformity and obtain perfect alignment
   b Retain by splint using Thomas type in case of leg or thigh fractures
   c X ray for position
   d Transport to a general hospital for definitive treatment
3 Fractures compound
   a Treat wound as in 1 omitting d and e
   b Treat fracture as in
4 Sprains
   a Shave injured part
   b Immerse in cold water or use ice bag
   c Dry
   d Paint with alcohol
   e Strap with adhesive

toward his rapid and complete recovery, resulting in his early resumption of work and pay

While factory accidents vary from the most severe to the trivial, it is the latter class which predominates In a well guarded factory the proportion of trivial to severe injuries is usually twenty to one Trivial

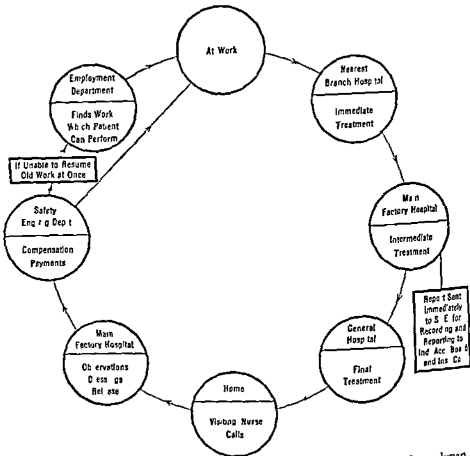


Fig 7 Accident cycle in severe injuries showing course of injured workman and points of contact with Health Safety Visiting Nurse and Employment Departments

injuries are potentially dangerous unless they receive early and proper treatment The standard form of treatment has been described in the Conference Board s outline[4] This form of treatment for open wounds is very satisfactory but not productive of quite so high a percentage of clean wounds as a soap and water wash and flooding with normal saline, followed by an antiseptic and a dry or sterile gauze dressing

An employee following an accident has two injuries one to his body and one to his mind The cure of the latter may be more difficult than that of the former An ambitious worker who wishes to return to work will cooperate in the treatment and progress much more rapidly than one who is apprehensive and uninterested in speedy recovery This latter type of worker must be encouraged and stimulated mentally his objections must be met and overcome and his progress toward recovery kept constantly before him It is important in the more severe cases to find very light easy work for him to do as soon as he is physically able in order to get him again into the working atmosphere and in contact with his fellow workmen

The treatment of the injured part must be carried out gently and physiotherapy employed as indicated Injuries usually require rest heat gentle massage and passive motion followed by active motion as soon as possible

Active motion produces more rapid cure than either of the first three forms of treatment mentioned and active motion which has an object such as the performance of a task is the most efficient treatment the patient can employ Graded work aimed to develop the physical ability of the patient is sought and as soon as he is able he should be transferred to work more closely allied to that which he was doing when injured The return of the injured man to his normal work is the goal toward which all treatment points Patients returning to work following illness are given a complete physical examination and, if found to be unable to do other than light work such work is arranged for with the Employment Department The foreman of the department involved is notified that the patient is not to be given any task other than that assigned until a change of work is approved by the doctor In some cases a permanent change of work may be necessary and the patient is told that he may never be able to do his former work

The Safety Engineer or Employment Manager assists the physician in planning for the reemployment of the injured man at work for which he will be physically fit in spite of his injury This cooperation is vital to the early and safe return to work of injured employees Where there has been serious injury with mutilation it may be necessary to provide prosthesis and reeducate as in the case of war cripples This training can often be done in the factory if there is a training or apprentice course in operation provided the manager of this course will give the injured man his careful and sympathetic attention In the usual type of accident no such course of training is necessary and the patient is placed at the

5 Burns
  a Treat shock, if present Give morphine by hypodermic
  b Cut away clothes from burned area
  c Apply wet saturated solution bicarbonate of soda to relieve pain Pat dry, then cover with sterile vaseline gauze and massive cotton pressure bandage
6 Foreign body in eye
  a Wash eye with boric acid, saturated solution
  b If foreign body cannot be removed with sterile gauze or cotton wipe anesthetize, using two per cent butyn solution Remove body with sterile cataract knife point, working with watchmaker's lens or the Berger loupe, and concentrated light
  c Drop fifteen percent argyrol or silvol in eye and advise colored glasses

Treatment is only a small part of the industrial physician's responsibility in accident cases He must so use his art and ingenuity in treating the injury that a minimum of tissue is sacrificed, a minimum of time is lost and the patient returned to work with as nearly normal function as possible This involves careful consideration of the type of work the patient was doing at the time of his injury, decision as to whether he can return to this work and if so, when he can return to it The foreman will wish to know these points as early as possible

Back Injuries —Back injuries seem to be increasing and to be more difficult to cure than in the past Bending the body to adjust a machine, lifting only a moderately heavy piece of work or even stooping to pick up something from the floor has been the cause of prolonged and recurrent disability Orthopedic examination frequently discloses symptoms and signs of pressure on the roots of the sciatic nerve on one side X ray of the back may show narrowing or wedging of the space between the fifth lumbar vertebra and the sacrum or of the space between the fourth and fifth lumbar vertebrae This indicates a diseased, degenerated or injured disc The exact diagnosis and the proper treatment is an orthopedic problem, but following treatment, conservative or operative the industrial physician must find adjusted work within the physical capacity of the worker This is in some cases difficult and unsatisfactory

Rehabilitation —This important step in returning the worker to earning capacity may be divided into mental and physical rehabilitation and the planning of a gradual return to his original work

4 To discuss sympathetically with him questions of compensation for his injury, to which he is entitled
5 To keep the patient under supervision until he has either returned to his original work or to the final type of work for which he is fitted

Sickness

Sickness is the most important factor controlled by the industrial physician The factory is really a community, and his position resembles that of the public health officer of a community Unlike the public health officer however he has to deal with individual as well as collective disease and his work is both preventive and curative

The most important functions to be carried out are

1 The isolation of contagious disease and the control of epidemics
2 The relief of trivial sickness
3 The diagnostic clinic

Contagious disease is not of frequent occurrence in factory practice where adults are employed The most important appear to be the virus diseases Urethritis and syphilis should be considered also but the matter of venereal disease will be taken up and considered later as a separate problem

When a case of contagious disease is discovered the patient is sent home and instructed to call his family physician The local Board of Health is notified and those who have been exposed are examined for signs of beginning disease Each employee in this group is instructed to report at the dispensary if signs of sickness appear

Various influenza epidemics have shown conclusively the devastating effect of a serious highly contagious disease upon factory workers Up to a short time ago no preventive treatment was available for influenza but recent experience with the administration of influenza A and B vaccine has been sufficiently encouraging to warrant its trial if and when an epidemic threatens Reactions do occur but these are seldom severe and the worker usually is not incapacitated for more than a day or two

Strangely enough the *relief of trivial sickness* is one of the most important functions of the industrial physician The economic loss from trivial sickness is much greater than supposed fully three fourths of the dispensary cases coming in this category and the industrial physician must always bear in mind the economic side of his work and consider these cases seriously If he can by early advice and treatment prevent

work he was doing when injured or at work as closely approximating it as possible. This usually provides easier work for the patient because of his past training and acquired skill. It is surprising to see how quickly a man will resume his full earning capacity even with a comparatively serious disability. The difficulty usually is in persuading him that he is able to resume work. This is particularly true of finger injuries which are very common. The worker feels that he will further injure the affected finger either by the work or by striking it against some part of the machine. Adequate protection can be given by the Brant splint or the tin crosspiece suggested by Manning. The machine worker is more or less inventive and can often devise some method by which he can handle his work for himself, if he is assured by the doctor that no injury to himself will result.

The special problems of accident prevention and accident compensation usually are in the hands of the Safety Engineer or of some one not connected with medical supervision. In some factories the doctor handles these problems as well as the medical work, but both prevention of accidents and compensation for loss of time because of accident are such specialized work it is better to have this handled by another department which should be in close contact with the Medical Department. The physician must, however, be fully informed of the Workmen's Compensation Act as administered in the State in which he is practising in order to talk intelligently with injured workers. The worker often will talk more freely with the doctor than with anyone else in the factory, and for this reason compensation points can be explained to him by the doctor with greater satisfaction than by some one in whom the worker has less confidence. If the doctor manages the compensation for, as well as the treatment of, an accident there is often a tendency on the part of the worker to distrust the advice given because of the doctor's part in the financial side of the transaction. This is to be avoided at all costs, for unless sympathy and cooperation exist between doctor and patient good end results and early return to work cannot be accomplished.

To sum up, the industrial physician's responsibility in accident cases is:

1. To render good surgical service.
2. To secure the best possible end result, both functional and anatomical.
3. To return the patient to some type of work at the earliest possible date.

this and a good but simple laboratory and careful enthusiastic workers *very satisfactory work can be done* It must be borne in mind that the object of this kind of work is diagnostic and not curative The diagnosis having been determined the patient should be given a concise description of the condition found and advice as to his mode of life habits and diet, when such advice is necessary He should then be advised to put himself in the hands of his family physician and a letter should be sent to his physician outlining the diagnostic findings and offering to assist in the treatment under his control This is a very delicate matter to handle from the point of view of professional etiquette but if tactfully managed proves of the greatest value to both doctor and patient In considering these cases of diagnosis the doctors on service should discuss the case check difficult points of the examination and cooperate in determining at the earliest possible moment the correct interpretation of the patient s condition

In addition to these types of medical work there is always a considerable amount of general medicine which must be practised Examinations must be made and treatment outlined for a large number of conditions neither trivial nor serious Many cases will present themselves where a specialist s services will be needed as in skin disease or diseases of the special senses Such cases may be diagnosed and treated at the factory dispensary or sent to a neighboring specialist In many cases of this type the dispensary and outside specialist can cooperate the specialist directing the treatment which is carried out at the dispensary while the patient continues to work The advantage of such an arrangement is that the patient loses no time from his work and the specialist knows that special or intricate forms of treatment will be carried out correctly under his control

The physician with vision will readily see the opportunities of doing preventive diagnostic and curative medicine under the factory dispensary plan Cases under special treatment can always be checked at a moment s notice by calling them to the dispensary Interesting or difficult cases can be reviewed at any time and owing to the fact that several doctors are usually on service, consultations may be held when necessary

The best method of meeting the *problem of venereal disease* has been broadly considered during the past year by the whole country in view of its importance to the army The factory community should be as free as possible of this type of contagious disease and every possible method should be used to keep it in abeyance The control lies in the physical examinations which discover cases among applicants for posi-

or reduce loss of time, he has gone a long way to convince both management and the worker that a medical department in the factory is of value An intelligent interest in, and sympathy with the trivial disorders of every day increases the confidence of the worker in the medical service being rendered and develops the habit of coming to the doctor at the first signs of sickness This is of great advantage as it enables the physician to observe a case from its earliest manifestation and in some cases to check the disease, even when of moderate severity, early in its course Moreover the careful record kept of these trivial sicknesses joined with the physical examination record, enables the doctor to gauge the constitution of the individual worker in a very accurate way Before the establishment of factory dispensaries this type of sickness was either totally neglected or often aggravated by patent medicines taken as a result of friendly counsel or self diagnosis The danger of this self medication has been shown repeatedly In no disease has the advantage of early diagnosis and the danger of delay and self medication been more strikingly proved than in pulmonary tuberculosis, a disease which in its early stages is manifested by symptoms considered trivial by the worker

The most common trivial sicknesses met in factory work are headache, constipation, subacute gastritis pharyngitis, tracheitis and coryza In a factory employing 5,500 workers the total number of medical cases treated during the year 1946 was 17 491 and the number of medical treatments 23 321 This means that, when a medical service is thoroughly established each worker will report on an average of three times a year for treatment

For the treatment of minor sickness a certain selection of drugs and appliances is indicated The general rule in factory work is to stock the smallest possible number of drugs and only add when sure that an *addition is* necessary The results obtained by the consistent use of a very small number of reliable drugs supplemented by an occasional prescription are excellent The appliances needed are such necessities as tongue depressors, throat applicators good drop lights several stethoscopes, one or more sets of an accurate blood pressure apparatus and the other instruments upon which the physician depends for diagnosis and special treatment

The factory employing three of four thousand workers presents a wonderful opportunity for a *diagnostic clinic* Comparatively little extra equipment is needed in the dispensary for carrying out an examination of difficult cases

The most expensive piece of apparatus is the x-ray machine With

Record Keeping

It is obvious that careful records should be kept of all cases applying to the main or sub dispensaries for advice and treatment A complete record of the physical findings at the primary examination of the applicant as well as records of any changes discovered on transfer or subsequent physical examination should be recorded on a standard card or sheet Almost every factory has a different method and a discussion of the various systems would take a chapter in itself[3] The experience of most industrial physicians is that the simpler the form used the better and that it is not so much the type of form as the thoroughness with which the routine notes are made which leads to a satisfactory set of records These records are of great value not only for the individual case but also for the studying of groups of cases having similar conditions By a carefully edited monthly report the chief physician can at a glance estimate the amount of sickness and accident which has occurred during that month and can compare it with that of the month preceding It is also possible to plot these results in such a way that interesting statistics are obtained

Follow Up System

It is important that a follow up system be carried out in rather minute detail Without this it is quite possible for cases to disappear and only be heard of through chance at a later date One of the simplest methods of handling this is to have the dispensary and sub dispensaries each keep a record book in which the name of the patient and his number is entered having a mark made against the date on which the patient is to return If the patient returns on this date the mark is crossed off and another is put down for a second visit which is crossed off in its turn on the patient s arrival If the patient fails to report the nurse can readily recognize his absence by the uncrossed line and will telephone the patient s foreman to send him to the dispensary If the man is absent from work the case is at once reported to the visiting nurse who investigates the case and sends a memorandum to the doctor of the result of her investigation

Supervision of Sanitation in a Factory

Factory Sanitation —The chief physician should have all the factory sanitation under his control the actual work being administered by a

tions, a routine blood test as part of the pre-placement examination re examinations of men being transferred from one department to another, of men reporting to the dispensary of their own accord and of men reported by others to their foreman and sent by the foreman to the dispensary for examination Occasional publication of leaflets for general distribution has proved valuable in arousing men to report for examination When a case is discovered, it is preferable to isolate the patient from factory work until noncontagious The treatment had best be carried out by an outside specialist, to whom all cases are sent, and who will keep the chief physician informed of the progress of the case In some large factories special clinics are maintained for these cases

Prevention of Industrial Disease

Each factory has its own occupational disease problem, and the analysis of this problem and the proper way of meeting it is one of the basic tasks of the industrial physician A mere enumeration of industrial diseases would take more space than this article will allow We will however, discuss the method by which the doctors should attack this problem The first principle is not only to discover occupational hazards but also to know the work at which the various departments place the workers By a careful investigation and a thorough comprehension of the work, the hazard can be definitely estimated and the type of man who is physically fitted for each department can be ascertained Any special hazards which are discovered should be investigated in a thorough and scientific way, and the workers who are exposed to this hazard should be kept under close medical supervision Where the hazard is due to an industrial poison, the workers should be examined frequently for that poison, a list being kept and the men called back at regular intervals to check their physical condition In this way any early signs of poisoning will be discovered and the occupation of the affected worker changed Where there is a general health hazard such as dust, those working in the very dusty departments should be examined annually and have chest films taken In all cases men who are exposed to occupational disease should be instructed as to symptoms which require a doctor s attention Cooperation with the Safety Engineer should be maintained, and with his assistance it is possible to reduce the health hazard

2 Hands should be washed prior to handling food
3 The housekeeping of the cafeteria should be regularly inspected by an industrial physician
4 Food if prepared in advance of serving should be cooled to room temperature in a space away from personal contact After cooling it should be placed in the refrigerator and transported cold to the stove where it is heated and served
5 Cream pies and mayonnaise are particularly likely to become infected and should be served immediately after preparation
6 Smoked and corned meat are very susceptible to infection and must be treated with special care
7 Soups and gravies must be kept at a continuous high temperature (180 F) until served

Such rules if carried out will minimize the posibility of food poisoning

Visiting Nurse Service

The Visiting Nurse Service has been mentioned several times and some of its duties pointed out The service should be under the control of the chief physician and the nurses under his personal orders The most important duty of the visiting nurse is the tracing of absentees Tracing has three different objects first to find out whether the worker is absent because of unreported sickness or accident second to give any immediate aid or nursing necessary third to report the cause of absence to the factory medical department if the absence is due to sickness or accident If the absence is due to a non medical cause the case is reported to the Employment Department

The visiting nurse also visits all cases of sickness or accident assigned to her by the Medical Department and reports the condition of each patient In addition to these specified duties the visiting nurse should be prepared to meet with promptness any emergency she encounters to advise workers where they may obtain hospital treatment for members of their families to give information about temporary homes or day nurseries for the children and to act as a social information bureau Besides this she is often used in the same nursing capacity as a district nurse when one is not available By her investigations the doctor is kept in contact with patients in the hospital and in their homes She is the medical connecting link between the factory and the home or hospital

To sum up the whole system the chief physician is responsible to

foreman as previously outlined The preservation of cleanliness in toilets locker rooms, work rooms, etc, testing and supervision of a pure water supply examination of ventilation and lighting conditions supervision of the disposal of sewage, reduction of pests and vermin, all these and similar matters should be part of the doctor's responsibility

Cleanliness of the toilets in a large factory is only possible when plenty of labor is available, for to keep toilets in proper condition they must first be made clean and then kept clean by inspection and labor

Most factories now provide a standard type of steel locker These lockers are satisfactory, but not unless each one is thoroughly cleaned before it is given to another worker

The examination of water is too technical a subject to be discussed here The same applies to the disposal of sewage

Flies and rats are the most frequent pests, and both can best be overcome by trapping Large fly traps placed between the factory and the breeding ground if the latter cannot be controlled, will have a marked effect on diminishing the number of flies in the factory This can also be controlled by DDT, 6 per cent, painted or sprayed around windows and doors and at the breeding sites

Cafeterias—When one or more cafeterias are in operation in a factory, the control of sanitation and the protection of food from infection is a responsibility of the medical department

Regular inspection combined with rules to govern cleanliness in handling food and the prevention of food poisoning are duties of the industrial physician

During the last five years food poisoning has occurred in a number of factories The number of workers affected usually was large The cause of such poisonings is infection of one of the foods by a staphylococcus or a streptococcus group The infection usually can be traced to one or more of the food handlers Frequently, the cafeteria worker, who is responsible, has no symptoms of harboring the bacteria The epidemic usually begins a few hours after the infected food has been eaten The patients present the picture of a very acute gastroenteritis with extreme nausea, vomiting diarrhea pain and prostration In some cases the patient requires hospital care but the majority are over the acute symptoms after six hours The patient is left very weak and may have indigestion for some time after The following cafeteria rules will reduce the possibility of such an outbreak

1 Food handlers should report to the medical department without delay for treatment of any sickness or minor injury

2. Hands should be washed prior to handling food
3. The housekeeping of the cafeteria should be regularly inspected by an industrial physician
4. Food if prepared in advance of serving should be cooled to room temperature in a space away from personal contact After cooling it should be placed in the refrigerator and transported cold to the stove where it is heated and served
5. Cream pies and mayonnaise are particularly likely to become infected and should be served immediately after preparation
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To sum up the whole system the chief physician is responsible to

the General Manager or Personnel Director He has as assistants, doctors and nurses, the former either part or full time workers, the latter full time workers The nurses in turn are divided into factory nurses who assist the doctors and are in charge of the main and dependent dispensaries, and the visiting nurses, who work primarily outside the factory

The chief physician is responsible for all matters pertaining to health, sanitation and nursing All such matters should be directly under his supervision In some factories part or full time dentists, psychiatrists and oculists are employed These usually act as specialists and only treat and diagnose cases sent to them by the chief physician

Medical Service for the Small Factory

While a high per cent of factories employing over a thousand workers maintain some type of medical service, similar but not as complete as the one which has been discussed the small factory has, for the most part, instituted no medical service for its employees

The problem may be met by providing a dispensary with a part time doctor, who has office hours, and a part time or full time nurse The doctor is on call for emergencies The work of the doctor and nurse should be supplemented by lay assistants who are trained by the doctor to give simple first aid at times when the doctor and nurse are absent and to act as a safety committee The duties of this committee are to inspect all parts of the plant, first with the doctor, later as a routine procedure, also to check on all hazardous exposures and operations The committee should also inspect all locker rooms and toilets and report unsanitary conditions

The physician taking on the medical work in a small factory must be tactful with people and have an interest in the maintenance of health in the factory community In order to do satisfactory work he should be taken on a survey of the factory by the superintendent Specially dangerous spots and any poisonous processes should be pointed out to him and he should be told of the product manufactured and shown the machines by which the work is done This will give the doctor a chance to estimate the hazards and the sanitary condition of the plant and to make his plans accordingly The doctor pays regular visits to the factory daily or once or twice a week, spending one or more hours depending on the size of the plant

At one of these visits he reviews the sanitary condition of the factory

and confers with the Safety Committee The results of his inspection and the committee reports are referred to the superintendent for any action necessary

At the dispensary he sees any cases of sickness or accident which have occurred since his last visit and treats or advises the patients After a month of this type of work he begins the physical examination of workers then employed beginning with the foremen and older employees and omitting any who object to being examined In this way the workers are gradually examined and each advised as to his condition At this time the doctor can arrange to take men off work for which they are not physically fitted, and to place them where, without loss of earning power they will be safer

After all the regular force has been checked new men recently added to the force can be examined shortly after hiring Unless the doctor is at the factory daily it is impossible for him to examine applicants for work before they are hired

Another method of meeting the problem of the small factory is a central dispensary near a group of small factories manned by a corps of doctors and nurses who serve the group of plants A doctor is sent daily to each of the subscribing plants supplementing the work of the full time nurse or trained assistant and carrying out the duties of the physician as in the first plan mentioned Applicants for employment in the subscribing plants are sent to the central dispensary for examination and more serious accidents or cases of sickness are transported from the individual factory to the central dispensary for treatment

Unfortunately although small plants employ over half the workers in the United States only a very small number provide medical service to workers except in the case of industrial accident Efforts have been made to develop inexpensive and effective plans in a number of cities without great success although these programs were initiated under excellent auspices and the principles backed by the approval of the National Association of Manufacturers[6]

INDUSTRIAL HYGIENE

The industrial physician in addition to the dispensary activities which have been discussed is responsible for the hygiene of the workers This involves a knowledge of those factors of environment which may affect the health and the efficiency of the workers and of the treatment of

conditions of the individual workers which may arise from such exposures These factors are classed under the heading of Industrial Hygiene

The conditions of factory environment which must be considered are heat fume, dust noise, light and ventilation

Heat—Many workers are exposed to great heat in the processes at which they are working The heat and work induce excessive perspiration As a result the body suffers from salt depletion Sweat contains about 0.25 per cent chlorides of which two thirds is sodium chloride If the loss of salt continues for long periods the organism is unable to retain fluids and this disability induces cramps in the muscles of the extremities and abdomen During this period of extreme salt lack the salt concentration in the urine falls far below normal The simplest method of prevention is the distribution to the workers of 10 grain salt tablets, two or three to be taken with water every three or four hours

Heat Stroke—This is rare in industry except among inexperienced workers There are prodomal symptoms of irritability and restlessness This may be followed by delirium and the patient become unconscious The skin is hot and dry The temperature is high (104°-105° F) The treatment consists of cool bathing or the cool spraying of wet sheets in which the patient is wrapped Cool enemata may be tried These measures are continued until the temperature falls to 102° or 103° F The patient should not be cooled to normal as the temperature may continue to fall after the baths are stopped See also Chapt XIX A Vol IV on Effects of Heat

Fumes—Workers may be exposed to a variety of fumes Fumes result from some chemical or physiochemical change Some fumes are very toxic, most are unpleasant It is good practice to have workers protected from inhaling fumes by locating suction pipes as close to the source of the fume as possible

Solvents—In many processes solvents are used If they are of a toxic variety, they present both a contact and a fume hazard Contact with the skin may produce dermatitis and inhalation of the fume may cause serious general poisoning For further discussion see Chapt XIX, Vol IV on Industrial Toxicology

To prevent intoxication by inhalation Moskowitz[8] suggests the following

1 Change of process or operation (substitution of less toxic for the more toxic substance)
2 Isolation either in time or space

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3 Control at point of origin of contaminant such as use of
   (a) local exhaust ventilation
   (b) wet methods for particulate matter
4 Dilution of contaminated with uncontaminated air by general ventilation
5 Good maintenance and good housekeeping
6 Use of personal respiration protective devices such as gas masks and respirators

Dust —Dust arises in many manufacturing processes and in mining Dusts may be divided into organic and inorganic dusts The organic dusts may be locally irritating when inhaled and in allergic workers may produce symptoms of hay fever or asthma Except for this they are apparently harmless Inorganic dusts may be either inert or harmful Most inorganic dusts are inert and can be inhaled in moderate amounts over years without producing any ill effect See Chapt XIV Vol IV on Industrial Hygiene for further discussion

The harmful dusts are those which contain some substance which when inhaled eventually produces incapacity The most important of the harmful dusts are those having a high percentage of free silica and the dust of asbestos The former causes silicosis the latter asbestosis In most cases the lower the per cent of free silica in a mixed dust the slower the lung reaction is in appearing

The important data to be obtained in any case of suspected pneumoconiosis are the character of the dust the quantity inhaled and the duration of exposure It is known that the majority of particles reaching the alveoli are from one to three microns in size If there is a high percentage of free silica in the dust if the dust is produced in large amounts and if the exposure has been one of years the chances of a silicotic reaction in the lungs are great

The symptoms of silicosis usually are slow in developing and consist of a dry cough and dyspnea The x ray picture shows nodulation of both lungs later the picture is that of fibroid phthisis with conglomerate masses and marked emphysema at the bases of the lungs

A worker may suffer only slight dyspnea with a chest showing nodulation by x ray and may be able to continue regular work for many years Incapacity is caused by the complicating emphysema or by active infection

Exposure to silica reduces the resistance of the lungs to the tubercle bacillus so that many silicotics develop a tuberculosilicosis

Hatch[9] has suggested the following standards of permissible dust

depending on the type encountered These standards are based on impinger samples, the dust particles being counted on a light field

KIND OF DUST	*Maximum Permissible Concentration Million Particles per cu ft*
Containing no silica	50
Containing any amount of silica, free or in combination	30
Containing 20 to 40 per cent free silica	10
Containing greater than 40 per cent free silica (preferably less)	5

Those workers exposed to asbestos inhale the fibres These fibres produce an interstitial fibrosis of the lungs which causes marked dyspnea and cough The x-ray picture is that of an interstitial fibrosis The symptoms of asbestosis appear to be far in excess of the pathology shown by the x-ray

While other dusts may produce shadows on the x-ray film, they seldom produce crippling disease, unless the underlying condition is complicated by infection See also in Chapt III in Vol II on Diseases of the Lung

Noise —This is an age of noise, and factories have every kind from the well known 'boiler makers" crash to the shriek of a driving belt The effect of noise, if the noise is severe and continuous, is deafness

The unit of noise is the decibel It is usually thought that anything over 100 decibels of noise is harmful to the ear, but in the textile industry as little as a continuous exposure to from 80 to 90 decibels produces symptoms The most common are headache, ringing of the ears and irritability Deafness is not usual unless the worker is exposed to over 100 decibels of continuous noise

The usual preventive measure is plugging the external auditory meatus with cotton which reduces sound about 10 decibels During the war experiments resulted in the reduction of 30 decibels of noise by the use of neoprene ear plugs which fit the canal tightly and are more comfortable than any previous moulded form of ear protection

Lighting—Modern factories are lighted largely by fluorescent lights in the ceilings These give a strong diffused light throughout the working area This light usually does not cause shadows and glare is avoided In cases where this type of lighting is not in use general semi direct supplemented by shaded individual lights probably gives the best practical results Each worker or group of workers can then control the light of the machine or group of machines being operated The light should fall on the work not on the operator s eyes There are three dangers to be avoided (1) over illumination or glare causing overstimulation of the retina and contracted iris (2) under illumination producing eye strain and (3) reflection from brightly polished metallic surfaces which tends to confuse and to have the effect of over illumination

Modern factory lighting endeavors to give good light, well distributed without glare Illuminating engineers point out that floor reflectance is too low for ideal results with indirect lighting Indirect lighting is considered the most desirable form of general lighting but one which may not be practical in factories The whole question of illumination is an engineering problem The industrial physician s interest lies in the effect that improper lighting may have on the workers

Ventilation and Temperature—There are various combinations of temperature humidity and air motion under which man feels comfortable but in no group will all persons be suited by any given set of conditions There is however a broad zone of conditions which satisfies the majority This zone is known by heating and ventilating engineers as the effective temperature and this is governed by the temperature, humidity and movement of air It is a comfort zone for the majority of workers and in factories varies from 66 F in winter to 71 F in summer

Ventilation is defined as ' the process of supplying or removing air by natural or mechanical means to or from any space The space being ventilated always will be contaminated by body odors smoke fumes or dusts These must be kept down by ventilation or by exhausts so that enough uncontaminated air is introduced to dilute sufficiently the contaminating substances and obtain comfortable working conditions Where there are no fumes and where there is no dust the amount of ventilation required for comfort and the elimination of odor varies from 7 to 25 cubic feet per minute, depending on the size of the room and the number of occupants

Fatigue—Workers in the past when heavy work and long hours were prevalent suffered from muscular fatigue At present with the

combination of short hours and the greatly increased use of mechanical substitutes for hand labor, physical fatigue is seldom encountered

Nervous fatigue is, however, a frequent phenomenon and occurs as a result of speed up pressure as well as from the tension of present day living Since nerve energy supplies the driving force for muscular activity, a worker suffering from nervous fatigue may complain of muscular fatigue, even though his task requires only moderate muscular effort

The fatigued worker is a special problem, and his work, his life and his temperament must be given consideration in deciding the best method of returning him to normal efficiency

INDUSTRIAL HYGIENIST

To control the various factors which have been outlined, large factories employ an industrial hygienist, who has the responsibility of studying and evaluating the health hazards to which the worker is exposed in his environment and of devising methods of protecting him from such contacts

The hygienist must know the chemicals or other harmful substances in use in the factory and develop methods of protection He must be able to determine whether or not the amount of contaminant in the air is dangerous or is below the danger mark and see that safe working conditions are maintained

His technical training must enable him to carry on the foregoing duties efficiently and intelligently He must be in close touch with the chief physician of the Medical Department so that his findings are known and so that frequent physical and laboratory examinations are made on those exposed to toxic or other harmful products His work necessarily will keep him in close contact with the Safety Engineer and the Engineer of the plant He should also develop a liaison with the State Department of Health which deals with problems of industrial health

INDUSTRIAL TOXICOLOGY

Certain substances used in manufacturing may cause irritation when they come in contact with the skin, others may cause poisoning if inhaled or ingested Dermatitis is a frequent cause of absenteeism from work and

is more prevalent than any other form of industrial disease However simple non irritating treatment combined with removal from contact with the offending substance will usually cure the condition in a reason able period of time

Toxic substances on the hands may be transferred to foods and thus ingested The quantity absorbed in this way is usually insufficient to produce poisoning It is by inhalation that the great number of toxic substances in industrial use produce their ill effects

Many toxic substances are used in modern production and new ones are being added steadily To enumerate these substances is impossible in this chapter and the reader is referred to Chap XIX Vol IV on Industrial Toxicology for detailed information

Substances are often not toxic to all exposed and an individual idiosyncrasy must be recognized Protection is afforded by careful engineering which traps the gas fume or dust at its source and removes it by suction In cases where this is not possible gas masks or respirators must be worn by the worker

Thorough washing of the hands before eating is a good preventive of ingestion of toxic substances and should be routine in a department Protection of the skin from irritants can be secured by the wearing of impermeable gloves the use of protective cream and the wearing of freshly laundered coveralls

ECONOMIC RESULTS OF THE WORK OF THE INDUSTRIAL PHYSICIAN

Industrial medicine has for its end two economic objects the reduc tion of disease and disability in the factory and the saving of financial loss to industry and to the worker The method by which the former is carried out has just been outlined its results will now be discussed before the second object is considered

In dealing with health statistics one is immediately confronted with a series of difficulties If we examine the number of medical cases apply ing at the factory dispensary for two consecutive years we may find more the second year than the first even though much preventive work has been done Such a condition might mean either an increase of sick ness or an increase in use of the dispensary by the workers In the same way a decrease of visits would be as likely to mean lack of use of the dispensary as any reduction of disease in the factory Probably the most accurate measure we can get is the time lost yearly from sickness and

combination of short hours and the greatly increased use of mechanical substitutes for hand labor, physical fatigue is seldom encountered

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while working but his in addition the loss in doctor s or hospital bills and the extra expense that sickness always entails

Another economic factor is the lowering of insurance rates for accident Insurance companies thoroughly recognize the advantage of a well organized medical department and its effect in reducing the insurance rates Most insurance companies will make an allowance for medical and surgical care which will meet a considerable part of the department s expense

These statements are borne out by statistics procured through a a questionnaire sent out by the National Association of Manufacturers in 1940 Heiser epitomizes the results of the 1600 answers as follows ninety two per cent of the companies replying said that their health program had reduced occupational diseases For 17 companies this reduction averaged almost 63 per cent 93 per cent of more than a thousand replies reported that compensation insurance premiums had been reduced More than 450 companies enjoyed an average reduction of approximately 29 per cent Nearly 90 per cent of 8 4 replies showed reduced labor turnover with 186 companies reporting an average reduction of 7 3 per cent[6]

The American College of Surgeons has standardized a minimum for Medical Service in Industry as follows

1 The industrial establishment shall have an organized medical department or service with competent medical staff including consultants and also shall have adequate emergency dispensary and hospital facilities and personnel to assure efficient care of the ill and injured

Membership on the medical staff shall be restricted to physicians and surgeons who are (1) graduates from an acceptable medical school with the degree of Doctor of Medicine in good standing and licensed to practice in their respective states or provinces (b) competent in the field of industrial medicine and traumatic surgery (c) worthy in character and in matters of professional ethics in the latter connection the practice of the division of fees under any guise whatsoever, shall be prohibited

3 There shall be a system of accurate and complete records filed in an accessible manner in the medical department such records to include particularly a report of injury or illness disability end results, as well as other information pertinent to the case or required by statute for Workmen s Compensation claims or other purposes

4 Patients requiring hospitalization shall be sent to institutions approved by the American College of Surgeons

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accident, but even this is very inaccurate owing to the rise and fall of number of workers employed, increasing and decreasing turnover and the difficulty of determining accurately whether the time loss is in reality the result of sickness

This method can be made slightly more accurate by dividing the time lost into three classes, time lost from sickness, time lost from accident and time lost for personal reasons The last may be considered a normal curve, and the rise or decline of the sickness and accident curves in comparison with this gives a more accurate estimate of the effectiveness of the dispensary

In considering the economic factor it must be remembered that production is the basis of industry Anything which interferes with production is considered an evil and will be dispensed with, if possible, anything which directly or indirectly increases production, is of value to industry and will be not only accepted but welcomed

Industrial medicine is a form of direct assistance to production by

1 Reducing turnover
2 Reducing the time lost from sickness and accident
3 Reducing the accident risk
4 Prolonging and increasing the working ability of workers physically below par

Turnover is a technical term used in industry to indicate the income and outgo of workers at a given factory There are several methods of computing turnover The most commonly used is that recommended at the Employment Managers Conference held in Rochester in 1918

Labor turnover is reduced by medical supervision because the worker is assigned to work for which he is physically fit, the attention to his sickness and accidents makes it an inducement for him to remain at work while correct heating lighting, ventilation and clean locker rooms and toilets make the factory a desirable place in which to work How much this reduction of turnover amounts to is very hard to estimate, for many other factors also must be considered It is recognized however, that medical supervision does reduce the turnover

The reduction of time lost from sickness and accident has been discussed already From an economic point of view this is of great value both to the employer and employee To the employer the less time lost the less costly and the greater the production, to the worker the less time lost the greater the financial gain Sickness to the worker is a double expense for he not only loses the money he could have made

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September 1 1948

5 The medical department or service shall have general supervision over the sanitation of the plant and the health of all employees[1]

SUMMARY

The function of industrial medicine is to provide medical supervision for industrial employees This supervision is based upon a knowledge of each worker's physical condition and of the environment in which he works

The industrial medical department through its pre placement examination selects the work for which the applicant is best physically fitted and reduces the chance of contagious disease entering the factory

Industrial accidents are promptly cared for, and the employee is followed until he is able to return to work, and when necessary, adjusted work is arranged which the patient can easily perform

Minor injuries are given careful attention so that the worker is able to continue his work while receiving treatment Cases of sickness are examined and given treatment, if the condition is trivial If more serious, the patient is referred to his family physician and not allowed to return to work without his doctor s permission All medical and surgical cases are recorded and the records kept immediately available

The industrial medical department has on record the health hazards in the plant to which the worker is exposed and reexamines those so exposed at regular intervals It is responsible for keeping the management informed of any condition in the environment of the worker which needs correction

Finally, its object is to assist in maintaining production by reducing time lost from sickness or accident and by its services to maintain a healthy working force

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CHAPTER XIX

INDUSTRIAL TOXICOLOGY

By EMIL BEYER, RONALD F. BUCHAN, JOHN H. FOULGER, HOWARD W. HAGGARD, ALICE HAMILTON, HARRIET L. HARDY, RUTHERFORD T. JOHNSTONE, CAREY P. McCORD, WILLARD MACHLE, MAX R. MAYERS, W. F. VON OETTINGEN, FRANK PRINCI, ADELAIDE ROSS SMITH, IRVING R. TABERSHAW, LUDWIG TELEKY

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BY WILLARD MACHLE AND EMIL BEYER

it is in this way that industrial poisoning from metals usually occurs A similar danger is the inhalation of finely ground dust

Skin absorption is important chiefly in connection with the coal tar derivatives aniline the nitrobenzenes the phenols and the compounds of toluene of which trinitrotoluene is the most widely known Others belong to the petroleum series methyl alcohol carbon tetrachloride triorthocresyl phosphate and others, which produce industrial poisoning both through fume inhalation and through skin absorption Naturally it is difficult to decide just what part is played by the skin in the case of a volatile compound because whenever there is skin contact there is also a possibility of fume inhalation but with regard to the coal tar derivatives skin absorption seems decidedly the more important During the two world wars there was opportunity to observe on an enormous scale the action of TNT on the human body and its mode of entrance This coal tar derivative can be absorbed both through the skin and through the air passages In World War I skin absorption seemed much the most important because of the increase of cases of intoxication whenever there was hot weather and the fact that amatol a mixture of ammonium nitrate 80 per cent and TNT 20 per cent was more poisonous than pure TNT Ammonium nitrate owing to its hygroscopic property keeps the skin moist and encourages skin absorption In World War II some observers laid the chief stress on fumes skin absorption was in their opinion of minor importance (see McConnell and Flinn[1])

Industrial poisoning by direct ingestion is of negligible importance Painters white lead workers makers of storage batteries may poison themselves by eating lead soiled food or getting lead on their chewing tobacco and it would be possible for men working with white arsenic or Paris green or the arsenates to be poisoned if they eat with unwashed hands Probably mercurial poisoning sometimes takes place in this way but such cases are neither so *common nor so severe as those that follow* exposure to fumes or dust

A second difference between industrial poisoning and non industrial is that the latter usually is acute the former usually chronic It is true that the occasional acute case of poisoning in industry attracts more attention because it is startling and it is clearly connected with the occupation while the chronic case is not dramatic and its connection with the occupation is often far from clear Nevertheless chronic cases are not only far more numerous than acute also they are sometimes more serious Acute benzene poisoning is very rare nowadays and if it does

I

INTRODUCTION

By ALICE HAMILTON

There are certain features in which industrial toxicology differs from general toxicology These may be grouped under three heads under the first of which would come the mode of entrance In ordinary poisoning the usual channel is through the mouth, the poison is swallowed accidentally or intentionally Next in frequency is the inhalation of poisonous gases, and the path through the skin is comparatively unimportant In industrial poisoning the relative importance of the different paths of entrance is quite different Inhalation of vapors, fumes and dusts is much the most important, then comes absorption through the skin, while the least important of all is ingestion through the mouth

Gases and vapors which enter through the respiratory tract, are very numerous in industry Some are compounds which have a direct local action on the tissues they reach The heavy acids may act in this way when, through some accident a spray of tiny droplets is thrown into the air This is also the mode of action of the nitrogen oxides and of sulphur dioxide, all of which have a caustic action, which may be confined to the upper air passages or may involve the whole lung tissue Other gases, without producing a local action, pass from the lungs into the blood In this group belong the asphyxiating gases, CO CO_2, HCN, H_2S, the petroleum distillates and a large number of petroleum derivatives and of benzene derivatives

The most dangerous form of arsenic is not white arsenic but hydrogen arsenide, which is given off in gaseous form, when one of the heavy acids usually sulfuric, less often hydrochloric, comes in contact with an arsenic-bearing metal zinc or iron, an accident not at all rare in industry Mercury volatilizes at room temperature and mercurial poisoning in industry usually is caused by inhaling volatilized mercury although absorption may take place also through the skin In poisoning from white phosphorus, fumes are chiefly important, although the poison may be conveyed also to the mouth by phosphorus smeared fingers

Metal fumes are finely divided particles of sublimed oxides produced by heated metals These enter the body through the inspired air and

poison for obviously a man can absorb more dust or fumes in ten hours than he can in eight Since indigestion with constipation interferes with elimination poor food becomes a factor of decided importance and since absorption is much more likely to take place from a fasting stomach the kind of breakfast taken by the workers in the poisonous trades becomes important The British pay far more attention to the feeding of their work people than we do and in the poisonous trades in England it is customary to provide a cup of milk or cocoa free of cost the first thing in the morning and to make it possible for the workers to get a hot drink usually tea with milk and sugar in the middle of the forenoon and afternoon and an abundant hot meal at noon In contrast to this a large number of American workmen in the poisonous trades especially those of foreign descent begin work in the morning on a breakfast of black coffee and bread and have nothing at noon but a cold dinner pail meal

The fact that individual susceptibility to poison varies very greatly is well known to toxicologists and always is clearly demonstrated in instances of mass intoxication such as the famous methyl alcohol poisoning in a Berlin lodging house from drinking adulterated brandy when some men died after drinking a quantity of liquor which in others caused only a passing attack of headache and dizziness In industrial poisoning this varying susceptibility is a very troublesome factor and causes confusion in the mind not only of the employer but sometimes of the industrial physician So long as the majority of a working force escape the effect of a given poison, it is very hard to convince the employer and sometimes the physician that the man who does suffer from its effects has anybody but himself to blame The employer argues that what is dangerous for one man must be dangerous for all that a falling scaffold a stream of molten slag an electric current produce the same effect no matter who is the victim Therefore if a dust or gas is harmful all the men should suffer from it He always can produce some old and seasoned workmen who have been with him for many years and have never been ill and he does not see why he should be responsible for the weaklings who do fall ill The industrial physician sometimes argues that if only a small proportion of the men react to a given poison it means that those men are more uncleanly in their habits or are alcoholics although a little investigation might prove to him that neither of these assumptions have any basis It is curious that men are so much more reluctant to accept this fact of varying susceptibility toward industrial poisons than they are to accept the equally startling variation in susceptibility to

not kill, it almost never leaves behind a lasting injury, but chronic benzene poisoning occurs with much greater frequency and is far more serious It is in the slow, chronic forms of mercurialism that we see palsies and psychoses, not in the acute, and the same is true of carbon disulfide poisoning

This is one reason why experiments on animals do not throw much light on the problem of industrial poisoning The acute effects may be reproduced fairly easily but not the effects of tiny doses repeated throughout the years

The third important difference between ordinary toxicology and industrial is that the former usually deals with one poison at a time, while the latter often has to deal with a mixture of toxic bodies, which produce a complex and confusing picture The temptation is to simplify, to pick out one poison and attribute all the symptoms to it, but error may lie that way For instance, a case of brass poisoning may be very much complicated by the presence of lead in the alloy Printers, who use type containing lead and antimony, and rubber compounders who handle lead oxide and the sulfides of antimony may, of course, suffer poisoning from either of these substances, but it seems hardly safe to diagnose a case of pure antimonial poisoning in such a workman and not to regard it as a mixed case Even more puzzling is the problem with regard to the mixtures of volatile poisons so much used in industry, the coatings, which contain members of the coal tar series and the fatty series the paint and varnish removers, the dry-cleaning mixtures and the great variety of compounds, which may be encountered in a single department of anilin dye manufacture Several studies on animals have shown that a mixture of poisons may be more potent than either alone Drinker's[4] work with the chlorinated naphthalenes (halowax) showed that carbon tetrachloride is a powerful adjuvant to these naphthalenes, Mytnick[3] found that benzolized animals reacted more promptly to carbon tetrachloride than to either if administered alone There was ample experience during the wars to prove that workers with TNT or with ether succumbed to a dose of alcohol that would not affect an ordinary man

Finally in considering industrial poisoning it is necessary to remember that there are factors in industry which distinctly favor the action of toxic compounds by lowering the resistance of the body increasing the possibility of absorption or interfering with elimination Heat and humidity help absorption through the skin and aid in the volatilization of the lighter poisons heavy work increases the amount inhaled by increasing the depth of respiration Long hours mean a large dose of

workers against occupational poisoning which it is hoped will be adopted by State legislatures

There is much vague evidence as to the greater susceptibility of women to industrial poisoning than men but little that is positive With regard to lead it seems clear that women if not actually more quickly poisoned than men (the two sexes rarely do exactly the same kind of work) are more subject to the severer forms of plumbism As to the other poisons benzene is the only one concerning which it can be said with certainty that it is more dangerous for women than for men this because benzene attacks the bone marrow which is more labile in women than in men and the hemorrhagic tendency in benzene poisoning is likely to cause in girls menstrual hemorrhage and in pregnant women abortion

Women are not more susceptible to the asphyxiating gases than men but the war time experience in England and in this country showed that young women suffered more from ether fumes than did mature men[6] The same impression holds in Germany with regard to the narcotic chlorinated hydrocarbons especially trichlorethylene Little is known about the effect on pregnancy of any industrial poison except lead and benzene but mercury has been found in the fetal blood as a result of poisoning in the mother

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infectious diseases Nobody attempts to explain the cases that occur in an influenza epidemic on the ground of the personal habits of the victims

Aside from this purely individual variation, there are certain factors that influence the incidence of poisoning How far race is a determining element we do not know Legge and Goadby speak of a factory in which Italian workmen show considerably less susceptibility to lead poisoning than do their English comrades, but this lasts only so long as they adhere to their national diet and do not become addicted to alcohol Negroes are considered by many practical men to be more susceptible to lead and less susceptible to poisons which enter through the skin, such as TNT, than white men, but it has never been possible to prove either of these theories largely because it has not been possible to compare two groups, whites and negroes, doing the same work and having the same living conditions In our TNT manufacture and shell loading during World War I it seemed at first that the negroes had decidedly less poisoning than the whites, but when both races had the same housing ate the same food and used the same bathing facilities, the apparent differences between the two disappeared, and the negroes had their full share of TNT sickness[4] The French experience with their munition poison dinitrophenol, was much the same as ours with TNT At first it seemed that the yellow race, the Annamites, were the least susceptible, and the whites were the most so But when they took into consideration the different standards of personal cleanliness, the greater amount of alcoholism in the white group and also the greater skill in diagnosis of the men in charge of the whites, they were forced to the conclusion that racial susceptibility had very little to do with it (Perkins[5])

It is unquestionably true that youth and immaturity influence the incidence and the severity of industrial poisoning This is recognized in all countries and embodied in legislation, wherever there is legislation for the protection of workers in the dangerous trades Practically all European countries provide for the exclusion of boys and girls from occupations which expose them to poisons In the United States such legislation has come more tardily, because it has never been the American habit to employ boys and girls in the poisonous trades and the danger has existed in only a few industries, such as printing type founding making lithotransfer paper, making lead seals soldering and using volatile solvents A committee representing the Federal Children's Bureau has formulated a model law for the protection of youthful

II

INORGANIC ACIDS AND THEIR ANHYDRIDES

By CAREY P. McCORD

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Antimonic acid
Antimonous acid
Arsenic acid
Arsenious acid
Bismuthic acid
Boracic acid
Bromoplatinic acid
Carbonic acid
Chloric acid
Chloroauric acid
Chloroaurous acid
Chloroplatinic acid
Chlorostannic acid
Chlorosulfonic acid
Chlorous acid
Chromic acid
Columbic acid
Fluosilicic acid
Germanic acid
Hydrazoic acid
Hydriodic acid
Hydrobomic acid
Hydrobromic acid
Hydrochloric acid
Hydrocyanic acid
Hydroferricyanic acid
Hydrofluoric acid
Hydrosulfuric acid
Hydrothiocyanic acid
Hypobromous acid
Hypochlorous acid
Hypophosphoric acid
Hypophosphorous acid
Hyposulfurous acid
Iodic acid
Iodoplatinic acid
Manganocyanhydric acid
Metaboric acid
Metagallic acid
Metantimonic acid
Metaphosphoric acid
Metasilicic acid
Metastannic acid (a and b)
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Molybdic acid
Nitric acid
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Orthoantimonic acid
Orthoantimonous acid
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Phosphoric acid
Phosphorous acid
Phosphotungstic acid
Platinic acid
Pyroantimonic acid
Pyrophosphoric acid
Pyrophosphorous acid
Pyrovanadic acid
Selenic acid
Selenious acid
Silicic acid
Stannic acid
Sulfonic acid
Sulfuric acid
Sulfurous acid
Telluric acid
Tellurous acid
Thiostannic acid
Tungstic acid
Uranic acid
Vanadic acid

Whenever foremost toxic actions center about the metal metalloid or other mineral components of the acid by long and justified practice physiological appraisal is contained in other chemical categories Obviously, *arsenious acid is more significant as one of the arsenic compounds* than as a mineral acid Silicic acid the immediate source of silicosis is more pertinently to be associated with silica as the cause of the occupational disease mentioned

On this basis of exclusion the few acids remaining, along with their anhydrides and a few selected compounds (not salts) closely *identified* with these acids are carbonic acid (carbon dioxide), the halide acids the nitrogen acids the sulfur acids hydrocyanic acid (by some accepted as an organic acid and herein elsewhere discussed) the phosphorous *acids*

Caustic Action of Acids

By no means are all caustics acids but all strong acids are caustics This action primarily is local since acids never act systemically as such The extent of caustic damage depends upon the individual acid its

The emphasis directed to the toxic properties of a few inorganic acids has long overshadowed the much larger number that comprise the total Therefore a listing is now presented which still fails to exhaust the possibilities

Antimonic acid
Antimonous acid
Arsenic acid
Arsenious acid
Bismuthic acid
Boracic acid
Bromoplatinic acid
Carbonic acid
Chloric acid
Chloroauric acid
Chloroaurous acid
Chloroplatinic acid
Chlorostannic acid
Chlorosulfonic acid
Chlorous acid
Chromic acid
Columbic acid
Fluosilicic acid
Germanic acid
Hydrazoic acid
Hydriodic acid
Hydroboric acid
Hydrobromic acid
Hydrochloric acid
Hydrocyanic acid
Hydroferricyanic acid
Hydrofluoric acid
Hydrosulfuric acid
Hydrothiocyanic acid
Hypobromous acid
Hypochlorous acid
Hypophosphoric acid
Hypophosphorous acid
Hyposulfurous acid
Iodic acid
Iodoplatinic acid
Manganocyanhydric acid
Metaboric acid
Metagallic acid
Metantimonic acid
Metaphosphoric acid
Metasilicic acid
Metastannic acid (a and b)
Metavanadic acid
Molybdic acid
Nitric acid
Nitrosyl sulfuric acid
Orthoantimonic acid
Orthoantimonous acid
Orthoarsenic acid
Orthophosphoric acid
Orthophosphorous acid
Orthosilicic acid
Perchloric acid
Periodic acid
Permanganic acid
Permolybdic acid
Persulfuric acid
Phosphamic acid
Phosphatomolybdic acid
Phosphoric acid
Phosphorous acid
Phosphotungstic acid
Platinic acid
Pyroantimonic acid
Pyrophosphoric acid
Pyrophosphorous acid
Pyrovanadic acid
Selenic acid
Selenious acid
Silicic acid
Stannic acid
Sulfonic acid
Sulfuric acid
Sulfurous acid
Telluric acid
Tellurous acid
Thiostannic acid
Tungstic acid
Uranic acid
Vanadic acid

Whenever foremost toxic actions center about the metal, metalloid, or other mineral components of the acid, by long and justified practice physiological appraisal is contained in other chemical categories. Obviously, "arsenious acid" is more significant as one of the "arsenic" compounds than as a mineral acid. "Silicic acid", the immediate source of silicosis, is more pertinently to be associated with "silica" as the cause of the occupational disease mentioned.

On this basis of exclusion the few acids remaining, along with their anhydrides and a few selected compounds (not salts) closely identified with these acids, are: carbonic acid (carbon dioxide), the halide acids, the nitrogen acids, the sulfur acids, hydrocyanic acid (by some accepted as an organic acid and herein elsewhere discussed), the phosphorous acids.

Caustic Action of Acids

By no means are all caustics acids, but all strong acids are caustics. This action primarily is local, since acids never act systemically as such. The extent of caustic damage depends upon the individual acid, its

concentration temperature and rate of dissociation Some acids exhibit avidity for tissue water some for oxygen Contrary to popular belief strong hydrochloric acid (40%) is only a mild escharotic, but strong nitric, sulfuric and sulfurous acids are immediate destroying agents

In the practical world of industry the chief threat from mineral acids is the "acid burn" The threat is real and has been met in acid using industries by special apparatus for acid handling, easily accessible showers for prompt body flooding after acid exposure, protective clothing and eye safeguards

The action of mineral acids on the teeth is not that of a caustic but as a solvent A concentration of acid borne by the stomach may not long be tolerated by the teeth Acids, notably sulfuric, little evaporate but may enter the atmosphere in steam It is not unusual for the long exposed acid worker to present teeth without decay or gingivitis but well and somewhat evenly worn down The teeth are softened and under the grinding of chewing are gradually worn down to stumps Protection apart from frequent air change in the work environment through mechanical exhausts, is difficult

CARBONIC ACID (H_2CO_3), CARBON DIOXIDE (CO_2) AND CARBONIC ANHYDRIDE (CO_2)

Since carbonic acid represents carbon dioxide dissolved in water, and since carbonic anhydride is a synonym, comment is limited to carbon dioxide

Carbon Dioxide

Common Physical Properties — CO_2, mol wt 44 carbon 27 27%, oxygen 72 73% an odorless colorless non flammable gas Sp gr 1 53 as a gas (air 1 0), as a solid 1 56^{-79}, boils −78 C 1 gm dissolves in 13 volumes of water at 25, less soluble in water at higher temperatures Temperature of "dry ice" −56 7° (5 2 atmos)

Some Industrial Exposures —

Alkali salt mfgs
Blacksmiths
Boiler room workers
Brass founders
Brewers
Brick burners
Caisson workers
Canners
Carbon dioxide mfgs
Carbonated beverage workers
Charcoal burners
Chemical mfgs
Coal miners
Distillers
Divers
Dry ice production workers

Some Industrial Exposures (continued) —

Drying room workers	Lime burners	Starch mfgs
(miscellaneous)	Lime kiln chargers	Stevedores
Dirt excavators	Linseed oil mfgs	Submarine workers
Farmers	Miners	Sugar refiners
Fertilizer mfgs	Paint mfgs	Tanners
Fire extinguisher mfgs	Pottery workers	Truckers
Firemen	Refrigeration plant workers	Vatmen
Freight handlers	Sailors	Vitamin mfgs
Furnace workers	Sewer workers	White lead mfgs
Golf ball manufacturing	Silo workers	Yeast mfgs
workers	Soda mfgs	

Toxicity —The propriety of rating carbon dioxide as a toxic agent is doubted Always it is the physiological stimulus to respiration In artificial respiration such as for the new born the apparently drowned or the electrically shocked carbon dioxide along with oxygen helpfully is utilized in concentrations up to 10% of the mixture Notwithstanding in the absence of direct toxic properties carbon dioxide is associated frequently with disasters and death both in and out of industry The response to carbon dioxide in high concentration rather than being characterized as a disease probably represents a normal reaction to an abnormal environment Carbon dioxide is a simple asphyxiant and may bring about all of the disturbances attributable to oxygen deficiency in the event it displaces oxygen and to the extent that it displaces oxygen However carbon dioxide is not so simple an asphyxiant as nitrogen since it does stimulate or overstimulate the respiratory center provoking dyspnea As an asphyxiant carbon dioxide leads yearly to a number of deaths or near fatalities such as from the accumulation of this gas in silos being filled with green ensilage from leaks in refrigeration plants where this gas is the refrigerant in mines where carbon dioxide is commonly termed black damp in open excavation work where pockets of this gas may be encountered in breweries as a result of grain fermentation in refrigerator cars where dry ice is used in cargo ships transporting fruit, in submarines etc Some deaths such as among sewer workers charcoal burners and boiler room firemen attributed to carbon dioxide are instead to be associated with more active gases such as carbon monoxide or hydrogen sulfide

In non fatal cases of carbon dioxide asphyxiation the dominant symptom is that of labored respiration but there may occur headache dizziness muscular weakness tinnitus profuse perspiration and mental excitement After the period of stimulation phenomena there comes evidence of impending death deep depression and coma

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Some Industrial Exposures —

Alkali salt mfgs	Caisson workers	Chemical mfgs
Blacksmiths	Canners	Coal miners
Boiler room workers	Carbon dioxide mfgs	Distillers
Brass founders	Carbonated beverage workers	Divers
Brewers	Charcoal burners	Dry ice production workers
Brick burners		

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March 1 1951

SULFURIC ACID SULFUROUS ACID AND SULFUR DIOXIDE

Minor Sulfur bearing Inorganic Acids

Hydrosulfuric	Nitrosyl sulfuric	Pyrosulfuric
Hyposulfurous	Persulfuric	Sulfonic

Sulfuric Acid

Common Physical Properties — H_2SO_4 oil of vitriol mol wt 98 08 contains 32 69 sulfur Concentrated commercial preparation represents 93% 98% acid the remainder being water Sp gr near 1 8 boils near 290 C, at high temperature the acid decomposes into sulfur trioxide This substance is a clear odorless liquid The apparent odor represents stimulation of the common chemical sense Fuming sulfuric acid is a mixture of H_2SO_4 and SO_3

No chronic state is known to exist, but chronic exposure may perpetuate the acute state. Sequelae may follow extensive exposure as a result of anoxia. Any portion of the body may be involved in sequelae but it is to be emphasized that exposures to moderately high concentrations of carbon dioxide never result in organic sequelae. The circumstances of carbon dioxide asphyxia accompanied by unconsciousness are strongly provocative of neurosis.

In "mountain sickness" carbon dioxide on a purely physiological basis enters into the causation of somatic and mental disturbances. At 14 000 feet the pressure of carbon dioxide in the lungs may be indicated by 28 mm of mercury, when at sea level the corresponding figure is 57. At the same time the pressure of oxygen in millimeters of mercury may be 53 in contrast to 100 at sea level. In this situation, in which carbon dioxide variation plays a role, the volume of breathing may have increased by 50%, and the rate of breathing may be excessive. While under these circumstances the production of carbon dioxide may be increased 6 or 8 times no justification exists for the culpating of carbon dioxide as the producing agent. The real etiological feature resides in physiological adjustment to low barometric pressure, lowered tension of both oxygen and carbon dioxide.

As a third aspect abnormal states related to, but not directly caused by, carbon dioxide derive from the fact that a high content of carbonic acid, such as in carbonated beverages, may dissolve metal, such as copper, in the processes of manufacture. Although copper plumbing is highly commended under ordinary usage, it may be unsuited when the substance passing through it contributes to metal solution.

Dry ice because of low temperatures alone instantly induces tissue freezing. This type of accident more often occurs among the general public than among industrial workers. However, by way of industrial occurrence it may be observed that in the manufacture of golf balls with hollow centers the process applied calls for the wrapping of rubber strands around small spheres of dry ice. Later the dry ice diffuses as a gas leaving the desired hollowness. Earlier rather than at the present time, uncautious workers incurred severe freezing of fingers. Any other substance at the same temperature would have produced the same degree of injury.

Sulfur Dioxide

Common Physical Properties — SO_2 (sulfurous anhydride sulfurous oxide) mol wt 64 06 contains 50 05% sulfur exists as a non inflammable irrespirable gas, at −10° C and atmospheric pressure condenses to a colorless liquid sp gr of gas 2 3 of the liquid 1 5, boils at −10 C and solidifies at −72° C related to both sulfuric and sulfurous acids Commercially it is supplied in compressed form in cylinders

Some Industrial Exposures —

Alkali salt mfgs	Dye makers	Pottery workers
Artificial ice mfgs.	Exterminators	Pyrites burners
Blast furnace workers	Feather workers	Refiners (metals)
Bleachers	Fertilizer mfgs	Refrigerator mfgs or repairmen
Bone extractors	Firemen	Storage battery chargers
Brass founders	Flue cleaners	Sugar refiners
Brewery workers	Fruit preservers	Sulfite cooks
Brick mfgs	Foundry workers	Sulfur burners
Broom mfgs	Fumigators	Sulfur dioxide workers
Candle mfgs	Galvanizers	Sulfurers (hops and malt)
Carbolic acid mfgs	Gelatin mfgs	Sulfuric acid workers
Cellulose mfgs	Glue mfgs	Sulfur miners
Chambermen (sulfuric acid)	Insecticide mfgs	Tannery workers
Chargers (zinc melting)	Lead smelters	Towermen (sulfuric acid)
Chromium tanners (2 vat process)	Mercury smelters	Ultramarine blue mfgs
Coke-oven workers	Oil flotation plant workers	Vulcanizers (rubber)
Copper smelters	Paper mill workers	Zinc smelters
Disinfectant mfgs	Petroleum refiners	

In addition to all of the foregoing sulfur dioxide is prone to appear in industry in numerous little anticipated activities For example in metal grinding with oils treated with sulfur or sulfur compounds for technological reasons the heat of friction may give rise to sulfur dioxide gas and thus provide an industrial exposure commonly foreign to metal grinding operations

Toxicity —Sulfur dioxide is one of the most active of the irritant gases and probably leads to greater pain than almost any other of the common industrial gases The order of its irritant properties is indicated in the table of physiological responses derived from Henderson and Haggard

Some Industrial Exposures —

Acid dippers
Acid finishers (glass)
Alum workers
Ammonium salts mfgs
Ammonium sulfate mfgs
Artificial leather mfgs
Benzol purifiers
Beta still operators (beta naphthol)
Brewery workers
Burnishers (iron and steel)
Candle mfgs
Carbolic acid mfgs
Carbonizers (shoddy)
Cartridge dippers
Cellulose mfgs
Chambermen (sulfuric acid)
Chemists
Color mfgs
Dimethyl sulfate mfgs
Dye makers
Electroplaters
Engravers
Etchers
Ether mfgs
Explosives workers
Fat purifiers
Felt hat mfgs
Fertilizer mfgs
Galvanizers
Glass finishers
Glue mfgs
Guncotton dippers
Hydrochloric acid mfgs
Hydrocyanic acid mfgs
Jewelers
Linoleum mfgs
Lithographers
Mercerizers
Nitrators
Nitric acid mfgs
Nitroglycerin mfgs
Nitrocellulose mfgs
Oil purifiers
Paint mfgs
Paper mfgs
Patent leather mfgs
Perfume mfgs
Petroleum refiners
Pharmaceutical mfgs
Phenol mfgs
Phosphoric acid mfgs
Phosphorous evaporating machine workers
Photographic workers
Picklers (metals)
Picric acid mfgs
Pyroxylin plastics workers
Rayon mfgs
Reclaimers (rubber)
Refiners (metals)
Salt extractors (Coke oven byproducts)
Scourers (metals)
Shoddy workers
Soap mfgs
Soda (Leblanc) makers
Storage battery workers
Sugar refiners
Sulfates mfgs
Sulfuric acid mfgs
Tallow refiners
Tannery workers
Temperers
Textile printers
Towermen (sulfuric acid)
Transparent wrapping material workers
Wax refiners
Wire drawers
Wood preservers
Yeast mfgs

Toxicity — Sulfuric acid in other than dilute solution is an active corrosive agent and solvent for teeth. Ordinarily it acts as such only on surface or contact tissues. It does not exist as the acid following penetration or ingestion. This substance is a frequent source of industrial chemical burns. Acid handling calls for continuous caution. Sulfuric acid little evaporates. It may be present in the industrial atmosphere in the form of a mist resulting from ebullition or chemical bubble formation such as in metal pickling.

Sulfurous Acid

H_2SO_3. This acid ordinarily represents an approximate 6% of sulfur dioxide in water. Slowly it decomposes to form sulfuric acid. It gives off sulfur dioxide and is offensive and troublesome on that account. Its action thus reverts to that of dilute sulfuric acid or otherwise sulfur dioxide now discussed.

atmosphere wherever sulfur bearing coal is burned in homes furnaces locomotives and water craft is sulfur dioxide In volcanic areas this dioxide regularly contaminates the atmosphere The minor respiratory tract disturbance around railroad stations, wherein coal burning engines enter is sulfur dioxide Many large industries such as smelters blast furnaces steel mills and open coke ovens, throw into the atmosphere great volumes of this gas At coal mines it is common that huge hills of slate and other mineral wastage but including a fair amount of coal are built up on nearby earth surfaces In time these combust and may burn for years These gob fires create volumes of sulfur dioxide gas along with other gases Particularly when fogs are present these may be carried down wind for long distances Associated hydrogen sulfide gas may blacken every lead painted surface Vegetation dies Silver ware is tarnished The sulfur dioxide is noticeable to most persons and widespread trivial degrees of irritation effect respiratory tracts Health damage is relatively unimportant but economic damage may be enormous Such conditions constitute a nuisance but not significant hazards to health

Sulfur Dioxide and Tuberculosis —Every irritant gas and some that are not irritant has been made the basis of claim alleging promotion of tuberculosis either providing conditions favorable for the action of the tubercle bacillus or otherwise accelerating tuberculosis already existing A fair number of court decisions may be located in which sulfur dioxide has been appraised as to causative or accelerative relationship to tuberculosis Scientific warrant for favorable decisions may be doubted and this statement applies to other irritant gases vapors and mists as well A few old experiments centered about the exposure of small animals to sulfur dioxide followed by the introduction of the organism of tuberculosis Between the test animals and their controls inconclusive differences appeared Among large groups of workers exposed to sulfur dioxide tuberculosis is no more prevalent than among comparable groups in other industries When on occasion sulfur dioxide induces a chemical pneumonia subsequent tuberculosis as a direct result is not prospective If this gas provokes long continued pulmonary tract inflammation to the point that a general bodily state of impairment and lowered resistance comes about this may have an influence on tuberculosis to the same extent as depletion of the same degree from any other non specific cause

Tolerance for Sulfur Dioxide —In industry it is common experience that workers long exposed appear to acquire a tolerance for sulfur dioxide and are little affected by it This is in contrast to the casual

	Parts of SO_2/Million Parts of Air
Least detectable odor	3 to 5
Least amount causing immediate irritation to the throat	8 to 12
Maximum concentration allowable for prolonged exposure	10
Least amount causing immediate irritation to the eyes	20
Least amount causing coughing	20
Maximum concentration allowable for short exposure (½ to 1 hour)	50 to 100
Dangerous for even short exposure	400 to 500

Sulfur dioxide is a fairly stable gas but in the presence of moisture is transformed to sulfurous and/or sulfuric acid. In foggy atmosphere both acid and oxide may co-exist. It is presumable that on reaching mucous membranes, the moisture there present combines with sulfur dioxide and that this extraction of water from cellular tissues is related to the irritation and the pain. This implies that the ultimate action is that of the sulfur acids. However, the severity of disturbance is greater than expectable from an equal quantity of preformed acid.

Symptoms. – In gross concentrations spasm of the laryngeal area somewhat effectively bars off the entry of the gas and gives rise to the term, 'irrespirable.' It thus comes about that the upper respiratory tissues may be more involved than the lungs themselves. From lower and commoner concentrations there may promptly arise inflammation of all membranes, violent coughing and sneezing, pharyngitis, laryngitis, bronchitis, pneumonitis with or without pulmonary edema. Bronchial pneumonia may arise. Among those long exposed there may appear digestive disturbances, impaired senses of smell and taste, excessive urinary acidity, increased fatigability and dyspnoea. Action is not limited to the respiratory tract and may involve the eyes. The skin is little damaged, but sulfur dioxide in water may provoke a dermatitis and a chronic state has been described resembling furunculosis.

The action of sulfur dioxide is not persistent so that a true chronic state does not arise except that chronic exposure perpetuates acute manifestations. On removal from further exposure all manifestations tend to disappear. However on rare occasions it is possibly true that a condition of allergy, or akin to allergy, develops to the end that subsequent trivial exposures excite responses out of proportion to those expectable.

Community Life and Sulfur Dioxide. – By no means is the import of sulfur dioxide limited to industrial workers. The chief irritant in all

tion and shock therapy suited to the same condition from any other cause As no specific treatment for this form of injury is known the treatment pattern ordinarily follows that for similar surface damage from other causes

Other conditions such as conjunctivitis may be treated symptomatically Fatalities are rare but functional neuroses long continuing are prone to arise One of the outstanding functions of the physician is to protect the patient from the beginning through psychotherapy against ensuing neuroses deriving from the patient s apprehensions in this alarming condition

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visitor in the same work area, who immediately coughs, sneezes, chokes and retches It is probably true that no genuine tolerance arises The worker as a result of continued exposure with resulting inflammation is protected by an outpouring of mucous secretion along the respiratory tract, which barrier serves to fend off immediate responses However damaging this defensive mechanism may be in the long run, it at least provides some degree of day-by-day comfort in the presence of this active gas

Tissue Freezing by Sulfur Dioxide—In some industries, such as refrigeration the sulfur dioxide employed is furnished in liquid form and thus at low temperature From minute leaks in the equipment tiny streams of liquid sulfur dioxide may spurt and instantly freeze sections of the eyeball or small skin areas Such eye injuries are consequential and call for care by the ophthalmologist Because of this risk all such workers should wear protective goggles

Treatment—Oxygen inhalation represents the best form of therapy for those more seriously involved Oxygen with 5% or 7% carbon dioxide has been advocated but not in the presence of pulmonary edema In gross involvement, respiration may cease calling for artificial respiration along with oxygen provision A new development provides intermittent oxygen supply without any traction on the lungs Respiratory sedatives are advocated to allay distressing coughing Whenever pulmonary edema appears and when there is any other significant involvement, complete bed rest is in order This should continue until all respiratory distress has disappeared Asthmatic attacks may arise calling for the judicious use of epinephrine and other bronchial dilators In general the treatment of pulmonary conditions resulting from lung irritants is much the same but added details may be found in sections devoted to chlorine, nitrous fumes, etc

Treatment for Sulfuric Acid Burns—Obviously the urgency for treatment will be somewhat determined by the concentration of the sulfuric acid and the surface area involved Since the prime action of sulfuric acid is related to its water demand all early treatment centers about water laving flushing and drowning Whether the water demand of the acid is met by external water or otherwise extracted by tissues, largely will determine the significance of injury The old practice of chemical neutralization constitutes no substitute for water flushing Subsequent application of mild alkalis or ampholites may be warranted but without great prospect of either benefit or harm After this stage surgical shock may be the demanding feature calling for shock preven

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Hydrochloric Acid Hydrogen Chloride and Chlorine

Minor Chlorine bearing Mineral Acids

Chloric	Chloroplatinic	Chlorous
Chloroauric	Chlorostannic	Hypochlorous
Chloroaurous	Chlorosulfonic	Perchloric

Hydrochloric Acid (Muriatic, Chlorhydric Acid)

Common Physical Properties –HCl Hydrochloric acid is a solution of hydrogen chloride gas in water, usually supplied in 38% solutions which form presents sp gr 1 18 . Be This described substance is a clear, colorless liquid possessing a pungent odor

Some Industrial Exposures –

Acetic acid mfgs	Cellulose mfgs	Glass mixers
Acid dippers	Chlorine compound mfgs	Glaze mixers (pottery)
Acid finishers (glass)	Chlorine mfgs	Glazers (pottery)
Alkali salts mfgs	Disinfectant mfgs	Glue mfgs
Ammonium salts mfgs	Dye mfgs	Hydrochloric acid mfgs
Aniline workers	Dyers	Ink mfgs
Battery (dry) mfgs	Electroplaters	Iodine mfgs
Bleachers	Enamel mfgs	Jewelers
Bromine mfgs	Engravers	Laundry workers
Bronzers	Etchers	Leather workers
Broom mfgs	Fertilizer mfgs	Lithographers
Camphor mfgs	Flour mfgs	Mercerizers
Carbonizers (shoddy)	Galvanizers	Methyl chloride mfgs
Cartridge dippers	Glass finishers	Munition workers

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Some Industrial Exposures — Occupations identified with HCl exposure are much the same as the aqueous solution already listed Hydrogen chloride represents the highly active form of HCl

Toxicity — Manifestations are to be linked with chlorine listed in following section

Chlorine

Common Physical Properties — Cl at wt 35 5 sp gr of gas 3 21 boils at −34 6 C freezes at −101 6 C, greenish yellow gas of pungent odor

Some Industrial Exposures —

Alkali salt mfgs	Dye mfgs	Rubber substitute mfgs
Beaterman (paper and pulp)	Extractors (gold and silver)	Rubber workers (synthetic)
Bleachers	Flour mfgs	Shoddy workers
Bleaching powder mfgs	Fumigators	Soda mfgs
Bromine mfgs	Ink mfgs	Sodium hydroxide mfgs
Broom mfgs	Iodine mfgs	Submarine workers
Calico printers	Laundry workers	Sugar refiners
Cellulose mfgs	Machinists	Sulfur chloride mfgs
Chemists	Nitric acid mfgs	Swimming pool (attendants)
Chlorine mfgs	Paper mfgs	Textile printers
Chloride of lime mfgs.	Phosgene mfgs	Tin recovery workers
Cutting-oil mfgs	Photographic workers	War gas mfgs
Detinning workers	Purifiers of sewage	Water purifiers
Disinfectant mfgs	Rayon mfgs	Zinc chloride mfgs

Toxicity — The use of chlorine as a war gas during World War I, together with studies on that gas subsequent to the war period provide an almost unequalled abundance of medical information on the nature and manifestations of chlorine action The studies of Gilchrist and others acceptably establishes that the occurrence of tuberculosis or acceleration of that disease is not facilitated by chlorine Likewise those earlier inquiries fail to prove that chlorine in highly dilute concentration exercises any substantial value in the prevention of respiratory affections It is possibly true that in work places harboring an atmosphere containing chlorine minor respiratory diseases may be of lower frequency If true this may be related chiefly to the destruction of organisms in the atmosphere later to be breathed rather than to any direct action on the respiratory tract tissues

Partly in error may be the common belief that chlorine reaching body surfaces merely reacts with the moisture there to [illegible] hydrochloric acid in the same fashion that hydrochloric [illegible]

Some Industrial Exposures (continued) —

Nitric acid mfgs
Paint mfgs
Paper mill workers
Perfume (synthetic) mfgs
Petroleum refiners
Phosgene mfgs
Phosphate extractors
Photographic workers
Picklers (metals)
Polishers and cleaners (metals)
Pottery workers
Rayon mfgs
Reclaimers (rubber)
Refiners (metals)
Sewage purifiers
Shoddy workers
Soap mfgs
Solderers
Steel wire drawers
Storehouse workers (Cl)
Sugar refiners
Sulphur chloride mfgs
Swimming pool attendants
Tannery workers
Textile printers
Tinners
Tin recoverers
Transparent wrapping material workers
Vignetters
Water disinfecters
Wire makers
Zinc chloride mfgs

Toxicity —Contrary to popular belief hydrochloric acid, even in concentrated form does not readily damage the skin Skin contacts, while not negligible, are far less hazardous than comparable exposures to nitric or sulphuric acid Henderson and Haggard have furnished the following table indicating the physiological response to divers concentration in the atmosphere of gaseous hydrochloric acid

	Parts of HCl/Million Parts of Air
Causes irritation of throat on short exposures	35
Maximum concentration allowable for prolonged exposure	10
Maximum concentration tolerable for a few hours	10 to 50
Maximum concentration tolerable for 1 hour	50 to 100
Dangerous for even short exposures	1 000 to 2,000

Aqueous hydrochloric acid as described is much less active than the gas, since the liquid has lost its dehydrating action, which is the basis of the outstanding damage from chlorine and hydrogen chloride Expectable symptoms from hydrochloric acid include, conjunctivitis, rhinitis, pharyngitis, bronchitis, solvent action on teeth and respiratory tract edema

Hydrogen Chloride

Common Physical Properties — HCl Mol wt 36 47, contains 97 23% of chlorine, sp gr 1 26, liquifies at −102 C In this form HCl is a colorless corrosive gas, fuming in the air with the formation of dense white clouds

Some Industrial Exposures.—Occupations identified with HCl exposure are much the same as the aqueous solution already listed. Hydrogen chloride represents the highly active form of HCl.

Toxicity.—Manifestations are to be linked with chlorine listed in following section.

Chlorine

Common Physical Properties.—Cl; at. wt. 35.5; sp. gr. of gas 3 1; boils at −34.6° C.; freezes at −101.6° C.; greenish yellow gas of pungent odor.

Some Industrial Exposures.—

Alkali-salt mfgs.	Dye mfgs.	Rubber substitute mfgs.
Beaterman (paper and pulp)	Extractors (gold and silver)	Rubber workers (synthetic)
Bleachers	Flour mfgs.	Shoddy workers
Bleaching powder mfgs.	Fumigators	Soda mfgs.
Bromine mfgs.	Ink mfgs.	Sodium hydroxide mfgs.
Broom mfgs.	Iodine mfgs.	Submarine workers
Calico printers	Laundry workers	Sugar refiners
Cellulose mfgs.	Machinists	Sulfur-chloride mfgs.
Chemists	Nitric acid mfgs.	Swimming pool (attendants)
Chlorine mfgs.	Paper mfgs.	Textile printers
Chloride of lime mfgs.	Phosgene mfgs.	Tin recovery workers
Cutting-oil mfgs.	Photographic workers	War gas mfgs.
Detinning workers	Purifiers of sewage	Water purifiers
Disinfectant mfgs.	Rayon mfgs.	Zinc chloride mfgs.

Toxicity.—The use of chlorine as a war gas during World War I together with studies on that gas subsequent to the war period provide an almost unequalled abundance of medical information on the nature and manifestations of chlorine action. The studies of Gilchrist and others acceptably establishes that the occurrence of tuberculosis or acceleration of that disease is not facilitated by chlorine. Likewise those earlier inquiries fail to prove that chlorine in highly dilute concentration exercises any substantial value in the prevention of respiratory affections. It is possibly true that in work places harboring an atmosphere containing chlorine minor respiratory diseases may be of lower frequency. If true this may be related chiefly to the destruction of organisms in the atmosphere later to be breathed rather than to any direct action on the respiratory tract tissues.

Partly in error may be the common belief that chlorine reaching body surfaces merely reacts with the moisture there present to form hydrochloric acid in the same fashion that hydrochloric acid is produced

Some Industrial Exposures (continued) —

Nitric acid mfgs
Paint mfgs
Paper mill workers
Perfume (synthetic) mfgs
Petroleum refiners
Phosgene mfgs
Phosphate extractors
Photographic workers
Picklers (metals)
Polishers and cleaners (metals)
Pottery workers
Rayon mfgs
Reclaimers (rubber)
Refiners (metals)
Sewage purifiers
Shoddy workers
Soap mfgs
Solderers
Steel wire drawers
Storehouse workers (Cl)
Sugar refiners
Sulphur chloride mfgs
Swimming pool attendants
Tannery workers
Textile printers
Tinners
Tin recoverers
Transparent wrapping material workers
Vignetters
Water disinfecters
Wire makers
Zinc chloride mfgs

Toxicity —Contrary to popular belief hydrochloric acid, even in concentrated form, does not readily damage the skin Skin contacts, while not negligible are far less hazardous than comparable exposures to nitric or sulphuric acid Henderson and Haggard have furnished the following table indicating the physiological response to divers concentration in the atmosphere of gaseous hydrochloric acid

	Parts of HCl/Million Parts of Air
Causes irritation of throat on short exposures	35
Maximum concentration allowable for prolonged exposure	10
Maximum concentration tolerable for a few hours	10 to 50
Maximum concentration tolerable for 1 hour	50 to 100
Dangerous for even short exposures	1,000 to 2,000

Aqueous hydrochloric acid as described is much less active than the gas, since the liquid has lost its dehydrating action, which is the basis of the outstanding damage from chlorine and hydrogen chloride Expectable symptoms from hydrochloric acid include, conjunctivitis rhinitis, pharyngitis, bronchitis, solvent action on teeth and respiratory tract edema

Hydrogen Chloride

Common Physical Properties — HCl Mol wt 36 47, contains 97 23% of chlorine, sp gr 1 26, liquifies at −10° C In this form HCl is a colorless corrosive gas, fuming in the air with the formation of dense white clouds

tract edema was either not present or not marked Dry rales existed on first examination In one group moist rales were recorded Evidence of cardiac damage was limited Dyspnoea persisted in a few patients up to 6 days

Routine laboratory examination revealed no outstanding features Fourteen of 33 patients acquired pneumonia in the diagnosis of which *roentgenograms were relied upon as the chief criterion*

Treatment —These patients were provided oxygen at the scene of the accident None was permitted to walk and effort was made to prevent all exertion At the hospital oxygen was continued under various forms of administration including positive pressure Oxygen therapy was continued for varying periods depending upon the condition of the individual patients As a prophylactic measure against pneumonia sulfadiazene and penicillin were administered the patients falling into three groups In the untreated group pneumonia appeared in 7 of 11 patients In the sulfadiazene group 5 of 15 patients acquired pneumonia In the penicillin group 2 of 7 patients presented that disease Sixty four per cent of the patients without chemotherapy exhibited pneumonia compared to 32 per cent among the combined groups subjected to chemotherapy The incidence of pulmonary edema apparently was not modified by chemotherapy being 75 per cent among the untreated and 77 in the treated groups

Aminophylline and epinephrine were administered as bronchodilators at various times after exposure with good results in the control of dyspnoea in some instances

No significant organic sequelae followed the acute events More than 50 per cent developed anxiety reactions with phobias lasting from 1 to 16 months No relationship was established between the severity of the early state and the incidence of neuroses No patients in the large group leading to the report here summarized required hospitalization longer than two weeks

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by the introduction of hydrogen chloride to water Chlorine is approximately twenty times as active as hydrochloric acid in provoking cell damage This increased capacity may derive from chlorine's extraction of hydrogen from moisture as an initial step and only most slowly lending itself to hydrochloric acid formation The order of physiologic responses to chlorine is indicated in the following table compiled by Henderson and Haggard

	Parts of Cl p pm of Air
Maximum concentration allowable for prolonged exposure	0 35 to 1 0
Least detectable odor	3 5
Maximum concentration allowable for short exposure (½ to 1 hour)	4
Least amount causing immediate irritation to the throat	15
Dangerous for even short exposure	40 to 60
Rapidly fatal for short exposure	1,000

Symptoms — The manifestations of exposure to chlorine above tolerable limits well conform to a pattern the severity largely being governed by the chlorine concentration and the duration of exposure The 1944 Brooklyn catastrophe while not involving industrial exposure, provides, through the report of Chasis and his associates adequate information as to symptomology physical findings and treatment

In this chlorine accident in 1944 a leaky cylinder in transportation discharged high volume of chlorine into a subway station beneath the street level at a time when a large number of individuals awaited subway transportation This station area thus took on the temporary character of a chlorination chamber Every element of a severe chlorination episode occurred ranging from mass hysteria to a few substantial cases of chlorine poisoning The total number of individuals present is unknown, but 418 were examined under hospital conditions Among those genuinely involved the early features were burning of the eyes with lachrymation burning of the nose and throat with rhinorrhea salivation, hoarseness coughing substernal pain and constriction In some there occurred nausea, vomiting headache and dizziness A few patients lost consciousness

Physical Findings — Among those hospitalized there appeared varying degrees of respiratory distress Cyanosis was common The majority presented moderate temperature elevation Upper respiratory

tract edema was either not present or not marked Dry rales existed on first examination In one group moist rales were recorded Evidence of cardiac damage was limited Dyspnoea persisted in a few patients up to 6 days

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	Parts of Cl p.p.m. of Air
Maximum concentration allowable for prolonged exposure	0.35 to 1.0
Least detectable odor	3.5
Maximum concentration allowable for short exposure (½ to 1 hour)	4
Least amount causing immediate irritation to the throat	15
Dangerous for even short exposure	40 to 60
Rapidly fatal for short exposure	1,000

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March 1 1951

Hydrobromic Acid, Hydrogen Bromide in Water Solution and Bromine

Hydrobromic Acid

Common Physical Properties – Hbr This acid is a solution of hydrogen bromide gas in water Various concentrations are purveyed The 34% concentration has a sp gr of 1 31, mol wt of hydrogen bromide gas is 80 92 sp gr 2 71 Hydrobromic acid in any concentration is a light yellow fluid that turns darker on exposure to light

Industrial Exposures – The industrial uses of hydrobromic acid as such are few in number apart from chemical laboratories and in the making of bromine compounds Wherever utilized in industry the significant exposure centers about bromine, which see

Bromine

Common Physical Properties – Br, atomic wt 79 9, sp gr 3 1, boiling point 58 7 C freezing point –7 C Bromine is a dark brown, fuming highly volatile liquid although commonly regarded as a gas

Some Industrial Exposures –

Bleachers of fibers and silk	Ethylene dibromine mfgs	Pharmaceutical workers
Bromine extractors	Explosives workers	Photographic film mfgs
Bromine salts mfgs	Extractors (gold)	Platinum extractors
Color mfgs	Ink mfgs	Tetraethyl lead mfgs
Disinfectant mfgs	Insecticide mfgs	War gas mfgs
Dye mfgs	Methyl bromide mfgs	

Physiological Response to Various Concentrations of Bromine (Henderson and Haggard) –

	Part of Br per Million Parts of Air
Maximum concentration allowable for prolonged exposure	0 1 to 0 15
Maximum concentration allowable for short exposure (½ to 1 hour)	4
Dangerous for short exposure	40 to 60
Rapidly fatal for short exposure	1 000

Toxicity —Bromine immediately and violently acts upon the skin mucous membrane leading to skin blisters and brownish staining and when inhaled even in low concentration produces prompt irritation along the respiratory tract coughing sneezing bronchitis and chemical pneumonia Although bromine is more active than chlorine the nature of such action is akin to that of chlorine as presented previously

Treatment —Treatment for bromine poisoning is precisely that for such other pulmonary irritant gases as chlorine While the treatment for all irritant gas poisoning is similar the violence of bromine action may call for more active or more prolonged therapy

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March 1 1951

Hydrofluoric Acid Hydrogen Fluoride in Water Solution and Fluorine

Hydrofluoric Acid (Fluohydric acid)

Common Physical Properties — HF, represents varying percentages of hydrogen fluoride gas in water usually about 4% A colorless fuming liquid not easily contained since it dissolves glass and ceramic ware No fixed physical properties

Some Industrial Exposures —

Aluminum extractors
Antimony fluoride
Antimony fluoride extractors
Art glass workers
Beryllium extractors
Bleachers
Brewery workers
Brick mfgs
Copper refiners and smelters
Dye mfgs
Electroplaters
Enamel mfgs
Etchers
Fertilizer mfgs
Fumigators
Gas (illuminating) workers
Glass etchers
Glass finishers
Gold refiners
Hydrofluoric acid makers
Incandescent mantle hardeners
Insecticide mfgs
Miners
Paper (filter) mfgs
Phosphate mill workers
Phosphorous extractors
Picklers (metals)
Pottery workers
Silicate extractors
Stone cleaners
Tank cleaners (brewery)
Welders
Yeast mfgs

Symptoms — Fluorosis is more definitely associated with fluorides as described later Otherwise hydrofluoric acid and its anhydride exert action precisely related to acid properties These are limited to surface tissues Manifestations include intense skin burning irritation of conjunctiva rhinitis bronchitis coughing ulceration of nasal tissues lips gums onychitis and paronychitis At the site of burns the skin or mucous membrane presents a hardened coagulated state The action of the acid is not quickly checked by the body so that destruction continues to the formation of deep ulcers

Treatment — Extent of injury from apparently small hydrofluoric acid burns is appalling Pain may be a constant feature Healing little responds to ordinary burn treatment The therapeutic procedures out

lined by Jones should be followed The damaged part if possible should be submerged in and rubbed with a warm saturated solution of sodium bicarbonate and promptly so Thereafter the damaged area should be massaged with a paste consisting of magnesium oxide and glycerine Shortly thereafter a 10% sterile solution of calcium gluconate should be injected into and beneath the escharotic area but the magnesium oxide paste should be continued over a period of days This paste represents - parts of glycerine and 1 part of magnesium oxide On occasion the destruction from hydrofluoric acid burns may call for the amputation of such members as fingers or the surgical excision of damaged areas on other parts

In the case of eye burns prompt and thorough irrigation with saline solution may aid followed by a local anesthetic suitable to eye application It is possible that the magnesium oxide ointment may be suited to eye application

Fluorine

Common Physical Properties — F atomic wt 19 sp gr 1 69 boils −187 C freezing point − 5 C a yellowish green gas of pungent odor decomposes many substances with violence

Industrial Exposures — Fluorine as such and hydrogen fluoride apart from hydrofluoric acid as such have few industrial applications Fluorine being the most active of elements and creating violence in contact with so many substances little lends itself to industrial manipulation apart from the laboratory These statements are not equally true for hydrofluoric acid The industrial exposure for fluorine is essentially the same as for hydrofluoric acid therefore reference should be made to the foregoing category

Toxicity — All of the acute manifestations associated with hydrofluoric acid would follow significant exposure to fluorine at even greater severity Apart from this acute state fluorine in the form of its salts (fluorides) produces a chronic condition fluorosis or fluorosine Within the scope of this section none of the salts of any of the acids discussed are explored as to industrial toxicity In the instance of chronic fluorine poisoning from fluorides it is recognized that the fluorine component regularly is responsible as the causative factor On this account fluorosis as derived from harmful exposures to fluorides will appear in another section

87 WHITE R P The Dermatergoses or Occupational Affections of the Skin H K Lewis and Co London 1934
88 ZEDERBAUM D Die Produktion von Brom vom sanitaren Standpunkte aus Behandelt X, 68, Gigiena Truda, 19 7
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Common Physical Properties — HF, represents varying percentages of hydrogen fluoride gas in water, usually about 4% A colorless fuming liquid not easily contained since it dissolves glass and ceramic ware No fixed physical properties

Some Industrial Exposures —

Aluminum extractors	Electroplaters	Insecticide mfgs
Antimony fluoride	Enamel mfgs	Miners
Antimony fluoride extractors	Etchers	Paper (filter) mfgs
	Fertilizer mfgs	Phosphate mill workers
Art glass workers	Fumigators	Phosphorous extractors
Beryllium extractors	Gas (illuminating) workers	Picklers (metals)
Bleachers	Glass etchers	Pottery workers
Brewery workers	Glass finishers	Silicate extractors
Brick mfgs	Gold refiners	Stone cleaners
Copper refiner and smelters	Hydrofluoric acid makers	Tank cleaners (brewery)
Dye mfgs	Incandescent mantle hardeners	Welders
		Yeast mfgs

Symptoms — Fluorosis is more definitely associated with fluorides as described later Otherwise hydrofluoric acid and its anhydride exert action precisely related to acid properties These are limited to surface tissues Manifestations include intense skin burning irritation of conjunctiva rhinitis bronchitis coughing ulceration of nasal tissues lips gums onychitis and paronychitis At the site of burns the skin or mucous membrane presents a hardened coagulated state The action of the acid is not quickly checked by the body so that destruction continues to the formation of deep ulcers

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March 1 1951

Hydriodic Acid Iodic Acid and Iodine

Hydriodic Acid

Common Physical and Chemical Properties — This acid is a solution of hydrogen iodide gas in water and may appear in various concentrations Thus it has no precise physical properties

Industrial Exposures — Apart from laboratory application and chemical manufacturing operation leading to the formation of hydriodic acid it has few uses and none introduce prospective harmful properties apart from iodine itself

Iodic Acid

Common Physical and Chemical Properties — HIO_3 mol wt 175 9 Little used in industry and no uses that introduce exposures apart from the action of iodine itself which see

Iodine

Common Physical and Chemical Properties — I at wt 126 9 sp gr 4 9 melts 113 5 C boils 184 4 C volatile at ordinary temperatures Exists as bluish black flakes and plates acrid taste characteristic odor

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arises which may progress to severe abdominal pain marked vomiting and diarrhea Regardless of the portal of entry iodine may lead to great thirst epistaxis and occasionally pulmonary and uterine hemorrhage The pulse rate is increased and the beat becomes near imperceptible Cyanosis occurs along with erythematous patches Hiccough dyspnoea and convulsive states infrequently arise After some hours the salivary glands may become sore and edematous The foregoing represents the acute form of iodine poisoning a condition little known to industry

Chronic poisoning likewise is scarcely known in industry but is fairly common in therapy from iodides A fair percentage of persons is highly susceptible to iodide action The commonest severe responses are related to the skin where widespread bullae may be observed as one form of skin damage Both in the acute and chronic form of iodine poisoning respiratory tract edema may be exhibited The gastrointestinal tract at any point or many points may become highly irritated Instead of salivation dryness of the mouth and throat has been observed Hemorrhage from any organ or tissue may occur including cerebral hemorrhage All these features and others related chiefly derive from clinical and not industrial exposure Just as the withdrawal of the drug is requisite in clinical practice removal from all further exposure to iodine and iodides is essential in occupational health work

Treatment — In the treatment of the acute condition starch or flour and warm water may be advisable when ingestion has been the portal of entry Swallowed solutions of sodium bicarbonate may have some virtue These substances lead to the formation of new iodine compounds which should be removed from the stomach by lavage The degree of pain may call for sedation Such substances as bismuth compounds may provide some degree of protection along the intestinal tract Cardiac depression may require treatment

Clinical experience would indicate that through continued low grade exposure a fair degree of tolerance may be acquired

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In the presence of moisture attacks metals and less actively damages organic substances

Physiological Response to Various Concentrations of Iodine (Henderson and Haggard) —

	Parts of Iodine per million parts of air
Maximum concentration allowable for prolonged exposure	0 1
Maximum concentration allowable for 30 minutes to 1 hour	0 5 to 1 0

Some Industrial Exposures —

Chemists	Intermediates mfgs	Pharmaceutical mfgs
Dye makers	Iodate mfgs	Photographic iodine mfgs
Fiber stainers	Iodide mfgs	Special soap mfgs
Germicide and antiseptic mfgs	Lithographers	Tanners
	Paper testers	

Medicine has so long relied upon iodine notably in the forms of the tincture and the iodides that common belief is that industrial exposures do not exist On a practical basis this belief is substantially warranted but at least potentially all of the evil properties of iodine encountered in therapy may be duplicated in industry chiefly in the chemical industries in the preparation of iodine and its compounds Iodine is a definite skin irritant Although ingestion is unlikely in industry as result of any work operation the order of iodine toxicity is suggested by the statement that less than two grams of elemental iodine may produce death (McNally) This stands in relation to the possible inhalation of dusts of iodine salts to the extent that iodine and its compounds may affect industrial workers The manifestations are similar to those better established through mishaps in iodine therapy

Symptoms — Unlike many harmful substances found in industry iodine may enter the body through all tissues including the skin On entry iodine combines in loose fashion both with fats and proteins In this form excretion through the kidneys may occur giving rise to renal and bladder irritation with the occurrence of albuminuria and rarely hematuria On contact surfaces iodine precipitates proteins and combines with the cellular content of hydrogen and alkalis Mild ptyalism is an early manifestation On ingestion gastric discomfort promptly

removal Ensuing dermatitis has been attributed to the dilute phosphoric acid but culpation probably should be directed to other constituents in the mixture such as butyl cellosolve The extent that dilute phosphoric acid serves therapy in man at once indicates low prospect of systemic injury in industrial pursuits Phosphoric acid as a source of phosphorus poisoning is unknown or dubiously known but operations attending phosphoric acid manufacture may provide exposure to phosphorus Apart from its effects as an acid, phosphoric acid introduces no outstanding exposures in industry

Phosphoric Anhydride

Common Physical Properties — P O Phosphorous pentoxide mol wt 142 04 contains 43 68% of phosphorus exists as white odorless amorphous, deliquescent powder In the presence of water it forms phosphoric acid In this process heat is evolved thus making handling dangerous

Some Industrial Exposures —

Chemists	Electric sign mfgs	Phosphorous anhydride mfgs
Electric light bulb mfgs	Nitrogen and other gas driers	

Symptoms — Expectable injury is limited to skin damage in the presence of moisture including both heat and chemical burns However the high content of phosphorus suggests the possibility of phosphorus poisoning from inhaled dust Its deliquescent property is little favorable to atmospheric dustiness

Phosphine

Common Physical Properties — PH_3 Hydrogen phosphide phosphuretted hydrogen (not to be confused with phosgene — $COCl_2$) Mol wt 34 0 sp gr 1 146 liquefies at atmospheric pressure and −85 C freezes at −132 5 C ignition point 100 C somewhat explosive This colorless gas provokes an odor of putrescence

Industrial Sources (Barillet) —

The action of phosphorus on alkaline substances in the presence of water

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PHOSPHORIC ACID PHOSPHORIC ANHYDRIDE AND PHOSPHINE

Minor Phosphorus-bearing Mineral Acids

Hypophosphoric	Phosphamic	Phosphotungstic
Hypophosphorous	Phosphatemolybdic	Pyrophosphorous
Orthophosphorous	Phosphorous	Thiophosphoric

Phosphoric Acid

Common Physical Properties — H_3PO_4 Orthophosphoric acid, mol wt 98 04, represents 31 64% phosphorus and 72 36% phosphoric anhydride (P_2O_5) Sp gr near 1 71 Exists as thick, colorless, odorless liquid with sharply acid taste At high temperatures (200 C) changes to pyrophosphoric acid and at still higher temperatures, to the meta state

Some Industrial Exposures —

Carbonated beverage mfgs	Engravers	Phosphoric acid mfgs
Chemists	Metal preparers (before plating)	Rubber latex workers
Confectionary mfgs	Pharmaceutical mfgs	Rust proofers

Toxicity — As a surface damaging agent concentrated phosphoric acid is on a parity with sulfuric acid of comparable strength Phosphoric acid dermatitis is well established but greater consideration should be extended to the thiophosphoric acid In the preparation of metal for coating phosphoric acid solutions have been directed to fingerprint

Concentration vol ( )	Duration of Exposure	Number of Exposure Days	Symptoms
0 001	29 h 5	4	Progressive poisoning died 6 h after last exposure
0025	5 h 10	3	No toxic effects survived
0025	10 h 40	3	Moderate depression later paralysis died 1½ h after last exposure
0025	12 h 10	3#	Progressive poisoning died after 1 days
01	3 h 28	1	Progressive poisoning died 12 h after beginning of experiment

These animals were exposed intermittently for different periods of time during each day
\# With 4-day interval

Physiological Response to Various Concentrations of Phosphine (Henderson and Haggard) —

	Parts of Phosphine per Million Parts of Air
Maximum concentration allowable for prolonged exposure	2
Slight symptoms after exposure for several hours	7
Maximum concentration that can be inhaled for 1 hour without serious consequences	100 to 200
Dangerous after exposure of 30 minutes to 1 hour	200 to 400
Fatal after exposure of 30 minutes	1 000 to 2 000

Symptoms — From the von Oettingen compilation phosphine poisoning in man is characterized by restlessness tremors excessive fatigability a tendency to somnolence thirst nausea vomiting gastric pain dyspnoea dizziness and substernal pain Later coughing may appear with or without pulmonary edema In dire cases coma and tonic convulsions arise Long exposure may eventuate in chronic poisoning identical or similar to phosphorus poisoning At autopsy findings may be scanty but on occasion pulmonary edema and cardiac dilatation with hyperemia of visceral organs may be demonstrated

Initial concentrations of phosphine harmful for man are little established Odor alone constitutes only a warning Various test papers

- The action of water vapors on phosphorus at elevated temperature
- The thermal decomposition of hypophosphoric and phosphorus acids and their salts
- The action of nascent hydrogen on elemental phosphorus, hypophosphoric and phosphorus acids
- The reduction of phosphoric acid by carbon at elevated temperatures
- The action of water on certain phosphides such as calcium phosphide and aluminum phosphide
- The decomposition of phosphides by acids
- The manufacture of calcium carbide and ferrosilicon, which may contain phosphides as contaminants

Some Industrial Exposures —

Acetylene workers	Phosphine workers	Seamen (occasionally)
Blast furnace workers	Phosphorous extractors	Submarine crewmen
Buoy mfgs	Phosphorous (red) mfgs	Vermin exterminators
Ferrosilicon workers	Phosphuretted hydrogen workers	Welders
Insecticide mfgs		

Physiological Responses in Cats (Von Oettingen) —

Concentration vol (%)	*Duration of Exposure in Minutes*	*Time of Death in Minutes*	*Symptoms*
0 005	105	240–300	Vomiting, superficial respiration, somnolence
0 015	160	160	Moderate depression dyspnoea, coma
0 017	120		1 survived, 1 died
0 03	45		Survived
0 03	120		2 died
0 04	30	55	Nausea rapid respiration dyspnoea, depression, twitchings
0 06	15		Primary stimulation then depression vomiting, recovery
0 25	25	51	Respiratory depression, pain, dyspnoea coma convulsions

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such as impregnated silver nitrate or 5% mercuric iodide, indicate the presence of phosphine gas at least in concentration at and above 2 p p m Different color reactions afford some quantitative evidence

More often than not phosphine arises under accidental conditions rather than as an anticipatable waste product of continuing industrial operation Notwithstanding all handling of ferrosilicon calcium carbide and phosphides should be conducted in such manner as to avoid moisture contact and storage should be associated with continuing ventilation Not all ferrosilicon will yield phosphine when wet

Treatment — For the treatment of phosphine poisoning which is rare in the United States there exists no precise therapeutic measures Oxygen inhalation is in order Non exertion is essential In the presence of pulmonary edema the administration of isotonic solutions is contra indicated Various stimulants may be favored on a symptomatic basis.

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Nitric Acid, Nitrous Acid and Nitrogen Oxides

Nitric Acid

Common Physical Properties — HNO_3, aqua fortis, mol wt 63 0? The fuming nitric acid represents a varying content of the nitrogen oxide, N_2O_4, along with HNO_3 Commercial nitric acid usually is of 68% strength

Some Industrial Exposures — Since nitric acid continually is potentially associated with its oxides, the industrial exposures below listed are to be regarded as common to these chemicals and will not be repeated in connection with the nitrogen oxides

Acid dippers
Aniline workers
Anthracine contracts
Aqua regia users
Artificial leather mfgs
Artificial pearl mfgs
Blasters
Bleachers
Camphor mfgs
Carroters (felt hats)
Cartridge dippers
Celluloid mfgs
Chemists
Collodion mfgs
Demascening workers
De brassers
Dimethyl sulphate mfgs
Dippers (guncotton)
Drugs mfgs (synthetic)
Dye mfgs
Dyers
Electroplaters
Enamel mfgs
Engravers
Etchers
Explosive workers
Felt hat mfgs
Fertilizer mfgs
Fur workers
Galvanizers
Gilders
Gold and silver separators
Guncotton workers
Insecticide mfgs
Jewelers
Lacquer mfgs
Lithographers
Metallurgical solvents mfgs
Miners (blasting)
Mordanters
Motion picture machine operators
Naphthalene mfgs
Nitrators
Nitric acid workers
Nitrobenzol workers
Nitrocellulose mfgs
Nitroglycerin mfgs
Nitrostarch mfgs
Nitrous oxide workers
Oxalic acid workers
Painters
Pharmaceutical workers
Phosphoric acid workers
Photoengravers
Photographic film mfgs
Photogravure workers
Picklers (metal)
Picric acid mfgs
Pyroxylin plastics workers
Rayon mfgs
Refiners (metals)
Rubber substitute mfgs
Rubber workers
Scourers (metals)
Smokeless powder mfgs
Soda mfgs
Textile printers
Sulfuric acid mfgs
Towermen (sulfuric acid)
Tunnel workers (blasting)
Welders
Wringers (guncotton)

Toxicity and Symptoms — While nitric acid may little be segregated from its oxides with respect to tissue damage, certain properties are closely related to its acid characteristics The present comment is limited to that phase Unlike sulfuric acid nitric acid does not possess tremendous avidity for water Therefore, the nature of the surface damage is

different. Nitric acid is a destroyer of proteins rather than a robber of water. Nitroproteins are produced. The tempo of action is slower so that prompt efforts at removal are likely to be somewhat more successful than in the case of sulfuric acid. The coagulum of nitroproteins has introduced a partial barrier to deep penetration. The area damaged becomes brown or yellow. Weak acid only produces this skin discoloration. Further effects related to acid qualities from nitric acid fume are irritation along the respiratory tract and eyes, sneezing, coughing, dyspnoea, chest pain and shock. More distressing manifestations such as pulmonary edema probably always are intertwined with the action of the nitrogen oxides always present and later discussed.

Treatment.—For surface damage the treatment is similar to that for sulfuric acid.

Nitrous Acid

Common Physical Properties.—HNO_2. This reddish acid represents an impregnation of nitric acid with certain of the nitrogen oxides. In combination with suitable bases this acid leads to the formation of the nitrates in distinction to the nitrates from nitric acid.

Toxicity.—Although readily dissassociated, nitrous acid is less active than nitric acid in protein destruction and the formation of nitroproteins. The similarity between nitrous and nitric acids is less definite than between sulphurous and sulphuric acids. The toxicity of nitrous acid is chiefly to be associated with its nitrogen oxide content and with nitrites. *Such items appear in other discussions directed to nitrogen oxides.* Methemoglobinemia may follow exposure to nitrous acid, but this action only further links this acid with nitrogen oxides and nitrites. Nitrous acid is so unstable that in most chemical reference books it is not listed as a chemical entity. In general its toxicity derives from its components.

Nitrogen Oxides

No fewer than five oxides of nitrogen exist. These are the monoxide (nitrous oxide) N_2O, nitric oxide—NO, dioxide (peroxide)—NO_2 or its dimer—N_2O_4, trioxide—N_2O_3, pentoxide—N_2O_5. Significance is to be attached only to three, the nitrous, nitric and to the

two forms of the dioxide one being dimer Nitrous oxide which is not without its toxic potentialities is without significance to industry This oxide belongs to the realm of anaesthesiology Nitric oxide – NO scarcely exists in the work room atmosphere since in the presence of oxygen and water vapor it is transformed but not instantly to the dioxide This fume possesses little or no irritant properties but is active in the creation of methemoglobinemia In some animal experiments exposure to this oxide in high concentration (1 00 p p m) has eventuated in little damage beyond excessive methemoglobinemia The form of nitrogen dioxide whether NO_2 or N_2O_4 is largely determined by temperature At 40 C the mixture is likely to represent 30 per cent of the NO_2 state and 70 per cent as N_2O_4 This is the mixture most likely to be encountered as a source of respiratory tract irritation and pulmonary edema In the presence of water N_2O_4 is altered to nitric and nitrous acids and NO_2 in the presence of water in the atmosphere shifts to nitric acid and nitric oxide Eventually the nitric oxide reaches the state of nitric acid In the presence of organic matter and at high temperatures nitric acid is changed to its oxide fumes Thus it comes about that the chemical trend of the oxides is toward creation of nitric and nitrous acid and at the same time under some circumstances these acids lend themselves to oxide formation The dioxide present along the respiratory tract through decomposition may yield for each milligram 0 55 milligram of nitrous oxide and 0 98 milligram of nitric acid, the high damaging factor Likewise the dioxide (per mgm), through decomposition along the respiratory tract, eventuates in the formation of 0 75 milligram of sodium nitrite In the course of sustained inhalation intake of a low concentration of the dioxide that is below the level productive of pulmonary edema relatively high quantities of nitrite may follow In this manner the road is now paved for two forms of pathological change depending upon concentration In the first, pathological change centers about pulmonary edema which may appear only after an interval of 5 to 24 hours and in the second centering about the systemic action of nitrites If the first action mentioned were not fulminating the second form of damage always would appear Actually the urgency of pulmonary edema with high prospect of early fatality obscures the nitrite phase

The physical properties of only one nitrogen oxide are here presented The properties of the other members of the series are similar but not identical Nitrogen dioxide has been selected

Nitrogen Dioxide

Common Physical Properties — NO mol wt 46 01 boiling point of liquid 21 3 C, freezing point of liquid −9 3 C Commonly this oxide as encountered in industry is a reddish brown gas However the color in part is determined by the degree of mixture with its dimer tetroxide ($N\ O_4$) which in turn depends upon temperature and pressure In the presence of moisture these oxides of nitrogen react to produce nitrous and nitric acids

Tolerable Limits of Exposure to Nitrogen Fumes — The oxides of nitrogen afford a classic example attending the difficulties of creating rigid standards for exposure to any substance Following tradition the literature is filled with statements specifying 39 p p m of nitrogen fumes as the upper limit of safety These oxides are measured quantitatively only through complex chemical procedures and no practical method might ever be expected to be accurate to the point that the exact figure of 39 would be justified If the origin of this figure be sought it may be traced to a publication in 1913 in a paper by Lehmann and Hasegawa following work begun in 1907 involving 14 cats 6 rabbits 3 exposures for one human investigator and one 5 minute exposure for another investigator *The method of quantitative determination is not above* reproach No less this one figure dominated the literature up to a period beginning about five years ago

Never advocating a rigid standard a more nearly unit standard rather than a zone might be justified if the quantitation of the nitrogen fume was an easy process if the same oxides in fixed percentages might be expected under all circumstances and if other harmful chemicals were not concomitantly produced Actually in the case of the formation of these oxides other toxic agents such as cyanides, nitriles and in the case of welding ozone may concurrently arise On these accounts adherence is not extended to any fixed limit of concentration with respect to the safety of those exposed However the two standards now widely influencing the situation are introduced

The American Standards Association has promulgated the following The maximum allowable concentration of oxides of nitrogen (calculated as NO_2) shall be 25 parts per 1 000 000 parts of air by volume, corresponding to 0 047 mgm per liter at 25 C and 760 mm pressure, for exposures not exceeding a total of 8 hours per day

Physiological Response to Various Concentrations of Nitrous Fumes (Henderson and Haggard) —

	Parts of Nitrogen Dioxide per Million Parts of Air
Maximum concentration allowable for prolonged exposure	10 to 40
Least amount causing immediate irritation to the throat	62
Least amount causing coughing	100
Dangerous for even short exposure (½ to 1 hour)	100 to 150
Rapidly fatal for short exposure	200 to 700

Symptoms — (1) Centering around pulmonary tract irritations Always with the focus on the dioxides it is to be emphasized that the action of these fumes is highly insidious and treacherous During the period of exposure there may be little awareness of pending disaster The devastating pulmonary edema is a delayed response The edema may appear within 3 or 4 hours or may not appear for 24 hours but experience is that 5 to 12 hours is the commonest interval Prior to the onset of edema there may arise minor irritation of the respiratory passages cough, dyspnoea chest pain and digestive disturbances Fleming observes that anoxemia may arise as an early manifestation antecedent to pulmonary edema and attributable to spasm of the terminal bronchioles Obviously anoxemia may reappear during the stage of pulmonary edema Cyanosis may constitute an outstanding factor

(2) Centering about the nitrite action When the exposure is to lower concentrations of the oxides and pulmonary edema is not present or does not determine the outcome a different series of manifestations may appear In this second type vasodilatation is present the blood pressure falls along with vertigo dyspnoea and cyanosis from methemoglobinemia and the extent of headache may be extreme Muscular tremors may be present rarely halucinations or convulsions In the chronic form blindness is a possibility on the least exertion tachycardia is noteworthy On occasion mild mannered persons may become quarrelsome even to the point of homicidal attempts In this condition a high degree of tolerance for further sustained exposure may develop Perhaps the best example of this form of nitrite action may be found in the well known 'dynamite head" When dynamite burns or explodes faultily, such gases may be formed as will cause extraordinary degree

of headache and at times as the sole manifestation of nitrite action The old time powder man is likely to slip a few grains of powder under his hat band to perpetuate his habituation over the weekend or during any period of absence from the work area

Von Oettingen recognizes three types of nitrous fume poisoning and describes them in the following language The reversible type of nitrous fume poisoning is characterized by dyspnea cyanosis vomiting vertigo somnolence a feeling of intoxication fainting loss of consciousness and methemoglobinemia This group of patients does not develop pulmonary edema and if removed early enough from the exposure may recover completely but otherwise the poisoning may end rapidly and fatally Some of the cases reported by Hall and Cooper (1905) Symons (1916) and Zadek (1916) may be classified in this group

With the shock type patients immediately show severe symptoms of asphyxiation convulsions and respiratory arrest death presumably being due to interference with the pulmonary circulation resulting in stasis in the blood vessels This form appears to be exceptional and may result from sudden inhalation of high concentrations Some of the cases quoted by Hamilton (19 5) may belong in this group

With the combined type the patient immediately shows symptoms from the central nervous system such as vertigo somnolence and staggering gait There may be some cyanosis After apparent recovery this stage may be followed after some hours by progressive dyspnea marked cyanosis and pulmonary edema as reported by Both (1936)

Sequelae of Exposure to Nitrous Fumes — In one sense pulmonary edema is a squela but more definitely are opportunities for chronic irritations of the eyes and upper respiratory tract the dissolving of dental enamel chronic bronchitis pulmonary emphysema alterations in the blood platelet picture pneumonia bronchiolitis obliterans cardiac dilation asthma and infrequently gastrointestinal dysfunction Obviously anxiety states and other neuroses readily may derive from episodes of poisoning by these oxides

Treatment of Pulmonary Edema — Within 48 or 60 hours pulmonary edema begins to abate Death from pulmonary edema which is the rule in severe instances usually occurs prior to 72 hours Oxygen is well indicated and in any significant exposure should be instituted immediately not waiting for the signs of pulmonary edema Artificial respiration rarely is necessary It may be harmful in the presence of pulmonary edema but on occasion may be required Intravenous introductions of saline or glucose ordinarily are without value To be effective oxygen

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should be administered through an inhalator and mask Mixtures of air and oxygen are superior to oxygen alone Above all absolute quiet and rest are requisite Patients only moderately exposed should not be permitted to undergo exertion The inhalation of ammonia vapors or chloroform is without value Experienced clinicians advocate venesection without the replacement of fluid removed Transfusions are contraindicated in the presence of definite edema but in some phases of the disease in the absence of edema may be warranted Sedation by barbiturates may be in order but morphine is contra-indicated The status of atropine in pulmonary edema is a matter of varied opinion The treatment of pneumonia or other mentioned sequelae should conform to the treatment desirable for the same state from other causes.

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III

ALKALIES

By ALICE HAMILTON AND RUTHERFORD T JOHNSTONE

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The alkalies used in industry are numerous and some of them are very powerful caustics, while all have more or less caustic action on the skin They present, however no problem to the industrial physician for their control is a matter of engineering skill and good plant practice and the lesions produced are evident to all The National Safety Council has prepared several pamphlets on the safe handling of caustic alkalies and the best method of treatment of alkali burns

AMMONIA

The fact that ammonia is a gas makes it more dangerous in industry than are the solid caustic hydrates Accidents from the bursting of an ammonia supply pipe in a refrigerating plant occur from time to time the severity of the effect depending on the time that elapses before the victims can escape Legge says that there were reported in Great Britain between 1920 and 1931 74 cases of acute poisoning from ammonia fumes all accidental and most of them caused by leaks or breaks in refrigerating plants and in plants recovering nitrogen from the air[1] According to Henderson and Haggard irritation from ammonia fumes begins at 0 5 mgm per liter of air coughing at 1 2 mgm but for prolonged exposure the limit should be 0 07 mgm It is however a matter of common knowledge that men become accustomed to the fumes to a considerable degree (Flury and Zernik[3]) Both Lehmann and Seifert found it impossible to produce chronic poisoning in animals but Ronzani[4] claims to have set up not only conjunctivitis but keratitis and also

a loss of hemoglobin and a lowered resistance to infection, while Horvath[5] goes even further and believes that pleurisy and bronchopneumonia follow the repeated exposure of animals to low concentrations of ammonia

Aside from refrigerating plants and the manufacture of refrigerators, ammonia fumes may be encountered in storage battery manufacture and in rubber vulcanization, but the fumes are not excessive Thies[6] says that as long as 10 days after an accidental injury to the eye from splashing of ammonia water a severe conjunctival and corneal ulcer may develop, and he describes such a case

General Measures of Treatment — "If liquid ammonia is spilled upon the clothing, all clothing should be removed immediately and the body thoroughly drenched with water The eye injured by ammonia should be washed immediately and copiously with water, and this may be followed by the introduction of a saturated solution of boric acid If pain is severe the use of a local anesthetic such as 0 5 per cent solution of pontocaine hydrochloride is indicated Thereafter the application of olive oil or some similar oil is desirable Continuous warm boric compresses to the eyes may be of value The usual treatment for corneal ulcers should be instituted, if this complication occurs, and an ophthalmologist should be consulted" R T Johnstone[7]

Respiratory and Circulatory Therapy — "If the concentration of fumes has been severe and respiration affected inhalations of from 5 to 7 per cent carbon dioxide in oxygen should be given, and if pulmonary edema ensues the use of oxygen by means of a tent or intranasal apparatus is advised The administration of such respiratory and cardiac stimulants as the following may be of value, coramine 1 5 c c, metrazol, gr 1½ to 4½ (0 1 to 0 3 gm) and caffeine sodium benzoate, gr 7½ (0 5 gm) Some of the respiratory and cardiac effects may be reflex in origin from the pulmonary bed and because of this the intravenous administration of atropine sulphate gr 1/75 to 1/60 (0 9 to 1 0 mgm), and papaverine hydrochloride gr ½ (30 mgm), might be of value These should be prepared freshly from the powders just before use" R T Johnstone[7]

Potassium and Sodium Hydrates

These are far easier to handle being solid and although caustic burns will occur if proper precautions are not taken the dangers are very well known in industry and the measures of prevention are well understood

Barium Salts

Bertarelli[10] has written one of the few articles on the possible action of barium compounds as used in industry It seems that in Italy barium chloride is used in treating wool for stuffing mattresses This renders it more elastic whiter and more resistant to moths He found that even prolonged work with carded wool which had been treated in this way never resulted in the inhaling of enough barium chloride to cause even a suspicion of toxic symptoms

Barium hydrate barium oxide and the sulphide are all mildly caustic

Chronic Poisoning from Alkalies

Chronic poisoning from the alkalies has been described only in connection with prolonged exposure to ammonia fumes and here the data are scanty Such exposure is encountered in stables and in refrigerating plants Ronzani[4] stated that animals exposed over a long time to 500 parts NH_4 per million developed anemia emaciation and showed a loss of defensive substances in the blood Horvath[5] exposed animals to 250 500 and 1,500 parts per million and produced with the lower concentrations, pleuropneumonia and with the higher catarrhal bronchopneumonia Some animals had also purulent inflammation of the upper air passages abscess of the lungs hemorrhagic infarcts etc On the other hand both Lehmann and Seifert (see Horvath[10]) found it impossible to produce chronic poisoning in animals

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IV

ACUTE AND CHRONIC FLUORIDE INTOXICATION (FLUOROSIS) AND FLUORIDE DENTAL PROPHYLAXIS

By CAREY P McCORD

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Hydrofluoric acid lends itself to the formation of numerous compounds both organic and inorganic Some inorganic forms such as cryolite (sodium aluminum fluoride) exist in nature but may be produced artificially while the greater number of industrially employed organic compounds arise from synthesis More definitely, toxicity is linked with inorganic salts Such artificial organic products as freon[1] (dichlorodifluoromethane) are essentially harmless[2, 3] Confusing the situation is the fact that certain fluorides are highly beneficent in the prevention of dental caries as brought about through the drinking of natural fluoride bearing waters of low fluorine content or through applications in the dentist s chair but at higher levels these same waters imbibed by children of susceptible age may induce dental fluorosis (mottled enamel) Dental fluorosis is not known to arise in industry Another anomalous feature derives from the apparent happening that in Europe chronic fluoride poisoning may be disabling while in the United States true disability is scarcely known Lastly before entering upon more detailed comment it may be observed that chronic fluoride

poisoning (fluorosis) bears little clinical resemblance to the acute state from the same agents.

Acute Fluoride Poisoning

Acute fluoride intoxication is more commonly identified with accidental and suicidal events rather than with regular occupational pursuits. This is exemplified by the Maryland catastrophe (1941)[61], the Meuse Valley disaster (1930)[171] and the suicidal records of McNally[145] and others. In the Maryland catastrophe 12 persons died and 40 others were *made violently ill as the result of eating pancakes in which sodium* fluoride intended for insecticidal use was substituted for baking powder. This type of accident has caused several political divisions to require that all fluoride insecticides be dyed a blue color or mixed with lamp black as well as labeled in the usual fashion for poisons.

In the Meuse Valley affair 60 persons died, and some thousands were made ill. The offender is believed to have been hydrogen fluoride. This fluoride is so closely akin to hydrofluoric acid as to stand apart from the nongaseous fluorides.

Fluorides are more readily available to the would be suicide than most chemical poisons since few restrictions are placed on the sale of insecticides.

In industry a commonly accepted tolerance level is 2.5 mgm per meter of workship air. More recent work tends to indicate that this seemingly liberal standard is still too stringent. In steel mills and smelting operations providing fluoride exposure somewhat above the limit mentioned, little is known to occur beyond nose bleed from direct inhalation and possibly an occasional chemical pneumonitis. Some industries report dermatitics from fluorides.

The usual entry into the body of nongaseous fluorides is by ingestion but inhalation of the dust is well known and absorption from mucous membranes is well proved. *Percutaneous absorption is not well* established.

As little as 0.2 gm has caused the death of adults but in the usual fatality from sodium fluoride from 5 to 15 gm have been ingested[145-171]. Sodium fluoride somewhat serves as the benchmark for the appraisal of the comparative toxicity of highly numerous other fluorides or fluorine bearing salts as sodium fluosilicate, sodium aluminum fluoride and ammonium fluoborate. The degree of solubility and, concomitantly, the rate of absorption are highly significant to toxicity.

Symptoms and Pathology.—Almost immediate burning along the upper alimentary tract may be noticed quickly followed by nausea vomiting (sometimes with bloody vomitus) and severe abdominal pain. Early salivation may appear along with marked thirst. Diarrhea may occur. At times involuntary defecation and urination takes place. Excessive sweating may be noticed. The fluoride output in sweat may be sufficient to induce skin discomfort in other persons handling the patient. Within a short time muscular paralysis arises. This first may be observable in the patient's inability to move about. Throughout this period the patient may complain of coldness and numbness. An early manifestation is dyspnea. The skin may be pale or cyanotic. Aphonia occasionally occurs. Pulmonary edema may arise particularly if the patient survives several hours. Such features progress to the point of unconsciousness with convulsive seizures and death from respiratory failure frequently ensuing within four hours[185]. Cases of less severity are likely to present some of the same symptoms in less pronounced degree.

All manifestations are believed to derive from three major actions. The first is to be associated with local corrosive damage, the second from deprivation of the body of calcium and the third with the inhibition of certain enzyme functions[9].

In the usual emergency so little time is available that laboratory work seldom is possible but blood chemistry would reveal low levels of calcium and urinalyses might indicate a level of fluorides in excess of normal. Some fluorides are always present in urine[100-102, 114, 118].

When the fluorine is in gaseous form such as hydrogen fluoride inhalation may lead to a somewhat different set of symptoms centering about profound inflammation of the respiratory tract, bronchitis, bronchiolitis and pulmonary edema[171]. If the inhalational intake be sufficient the eventual systemic effects may be the same as from ingestion.

At autopsy marked inflammation with erosion and edema may be established along the gastrointestinal tract following peroral intake. The lungs may present edema. Hemorrhagic areas may be found anywhere including the skin. Such hemorrhage may be petechial. Subsequent chemical examination of postmortem material may reveal the fluoride in most organs and tissues[145].

Treatment.—If fluoride be established or suspected as the cause and if the intake be peroral, copious gastric lavage should be undertaken with lime water or weak calcium chloride. This is for the purpose of converting soluble fluorides into the inert, insoluble calcium fluoride.

Calcium gluconate or other suitable calcium solution should be intro duced intravenously as a step immediately after gastric lavage Fluids such as salines should be introduced early In animal work aluminum sulfate has been found to serve in counteracting sodium fluoride action So also boric acid leads to the formation of the less toxic fluoborate[10]

Other treatment is symptomatic, including administration of oxygen in respiratory failure

Chronic Fluoride Poisoning (Fluorosis)

For some centuries it has been known in certain volcanic countries and notably Iceland that cattle are prone to develop a strange malady involving the bones and teeth for long periods after volcanic eruptions Only in modern times has explanation for this happening been accom plished The volcanic output included large volumes of gaseous fluorides and presumably hydrogen fluoride This gas was absorbed or adsorbed by volcanic dust and transported into far reaches There the dust settled on growing vegetation or the earth Vegetation immediately or subse- quently so contaminated eaten by cattle produced chronic fluorine poisoning a disease known to animal husbandry and accorded a dozen colloquial names such as "gaddur and darmous"

In comparatively recent years a similar condition has been detected in man from a dissimilar mechanism but related chemicals, termed "dental fluorosis or mottled enamel The import of this condition leads to a separate section on a following page

Still further chronic fluoride poisoning has appeared in industry and is termed fluorosis This condition is attributed to the slow intake of fluorides at a level well below that associated with acute poisoning but at such level as to provide storage or at least cumulative action Some text books ascribe to this condition a set of symptoms merely ex- tending low grade acute manifestations into a chronic state More realistically fluorosis is highly dissimilar in its characteristics Fore mostly it is marked by osteosclerosis and calcification of tendonous tissue Cachexia and anemia have been described Clinically the condi tion may resemble arthritis or arthritis deformans[10]

The description by Moller and Gudjonsson of Copenhagen[147] is introduced but in our own translation These investigators studied 78 workers out of 100 employees in a cryolite mill preparing natural cryolite (sodium aluminum fluoride) They state

In the course of the investigations it was noted in the study of the x ray pictures that many of the chest films showed a peculiar opaqueness and density in the rib shadows collar bones and cervical vertebrae which deviated noticeably from the ordinary delineation of the bones More over it was noticed that a considerably longer exposure was required properly to bring out the pictures In the systematic investigation of the bony system of the workmen it was found that 30 of the 78 who were studied showed bone changes of different degrees and of different extent in the most severe cases massive alterations in the structure and the de lineation of the bones most noticeable in the spongy portions, were encountered

Upon studying the pictures of the spinal column and those of the pelvis one first notices the almost complete disappearance of the osseous structure this is obscured by what appears on the original films to be a milky white opaqueness At some points the structure still shows through the individual bone callosa which are present are how ever thick dense and obliterated by woolly structures Likewise the outlines of the vertebrae are shown indistinctly If one desired to com pare the appearance of the individual vertebrae with a known disease this would most nearly give the picture which one finds in the case of the productive metastatic carcinoma of the vertebrae associated with a primary carcinoma of the prostate

Not only are the bodies of the vertebrae altered but also the trans verse processes are plump thick and covered with small protuberances the spinous processes show through like a thick broad irregular band which one can follow almost unbroken through the middle of the whole spinal column This is partially caused by the fact that the tendons and attachments of the ligaments are the foci of extensive calcification in the severe cases The lateral and anterior ligaments o fthe spinal column with their calcifications almost form bridges between the vertebrae as one finds them in the case of severe forms of spondylitis At certain points these calcifications can produce pictures that completely resemble arthritis deformans All around the joints of the spine and the joints between the ribs and the vertebrae there are formed large bony protuberances

Particularly the posterior attachments of the ribs are covered along their borders with large irregular hoarfrost like protuberances which are caused by calcifications in the points of the attachment of the inter costal muscles The density of the shadows of the ribs with the decided calcification of the costal cartilages are noticeable

If we consider the pelvis we find here the same opacity and density of the bone Here also the outline is not definite and is covered with either sharp or plump calcifications corresponding to the points

where the muscles are attached The ischio sacral ligaments are decidedly calcified great calcifications are also found as low as the points of attachment of the adductor muscles

In the extremities one sees the solid bone substance considerably thickened and the medullary canals reduced in size The normal bone margins are prominent and are covered with cotton like calcifications and sharp protuberances At the points where the large muscles are attached one sees large irregular calcifications of the tendons The small bones in the hand and foot resemble the vertebrae but are less dense

In the most severe cases one also finds changes in the skull but in general the thickenings are only slightly developed in the skull bones

As will be seen from the description all of the bones have been attacked in the severe cases However the intensity of the change decreases from the center to the periphery and is greatest in the spinal column and the pelvis at these points one can discover the first stages of the thickening in the form of a wooly thickening of the bone callossum and greater density of the bones in the x-ray film In the second stage of the disease the real opacity of the bone pictures begins to be apparent bone margins proliferate and one can generally see also the beginnings of an increase in density in the extremities However one cannot draw a sharp line between the different stages of the disease

It is not known to what concentration of fluorides the aforedescribed cases were exposed

In a few publications disability is associated with fluorosis Roholm[16 11] describes three states of modified bone density from fluorides as follows

1 Incipient increase in the density of bones
2 Pronounced increase in bone density with incipient or moderate calcification of ligaments
3 Marked increase in density accompanied by bony hyperplasia with or without calcification of ligaments

Disability has been noted only in those individuals involved in the third stage

In this country Largent Bovard and Heyroth[104], in material now in publication and based on extensive investigation of workers exposed to fluorides, reach the conclusion that disability is little expectable from fluorosis These authors are unable to account for the apparent lower severity of involvement in this country compared with some other portions of the world Categorically they state Data so far available concerning residents of the United States do not reveal any evidence

of disability associated with changes in bones that have resulted from exposure to fluoride

Largent and his associates after presenting extensive tabulations related to urinalyses roentgen examination etc conclude that a definite correlation appears to exist between the level of the fluoride concentration in the urine and the presence or absence of changes in bony density With reservations they present 10 mgm per liter of urine as the level above which bone density changes may be expected and below which such changes might not occur No correlation was established between the length of employment and the appearance of bone changes The age of workers appeared to be without significance as to prospective bone changes

Prolonged drinking of water bearing fluorides above 1 p p m usually induces nothing more than dental fluorosis or at least little attention has been attracted to finding other than dental fluorosis From 114 examinations however Dean[16] has encountered and reported 13 cases of increased bone density from the consumption for periods of 19 years or longer, of drinking water bearing 8 p p m of fluorides All determined some 20 cases of fluorosis have been recorded as having occurred in the United States and all without disability[104]

At this time chronic fluoride poisoning of the type termed ' fluorosis must be accepted as a disease entity but much further investigative work is required before final appraisal may be made of this state whether it occurs among workers or among the general population from the consumption of water or food with excessive fluoride content

Dental Fluorosis (Mottled Enamel) and Fluoride Dental Prophylaxis

Dental enamel a modified bony tissue is peculiarly responsive to the action of fluorides during early life So common is this affection in some portions of the world but chiefly in some areas of the United States that warrant exists for its segregation as a pathological entity Customarily dental fluorosis is attributed to the imbibition of water containing more than 1 p p m of some inorganic fluoride usually sodium fluoride All food contains fluorides and in the aggregate may reach the level that in water would attract attention Yet fluorosis solely from normal food intake is unknown Machle and others[113], however, believe

that food fluorides may not be ignored as a factor in the causation of fluorosis

How long dental fluorosis has been observed is uncertain, but apparently the condition was first appraised medically by Eager[58] of the United States Public Health Service On a tour of duty in Italy he observed mottled enamel in Italian migrants and particularly in those deriving from Pozzuoli In 1916 Black and McKay published the first observation of this condition in the United States[12, 143] Later, McKay[13, 144] presented numerous publications based on first-hand observations, and still later Dean[41, 52] made notable contributions to the extent that the investigations of these three workers may be regarded as the classical background of the topic

In ensuing years inquiries have been directed at almost every portion of the world resulting in the knowledge that practically every country possesses some areas in which the water supply contains fluorine in sufficient concentration to produce dental fluorosis[3, 4, 7, 30, 71, 72, 93, 123, 138, 141, 15, 154, 211] Australia is said to be the one exception since as yet highly fluorinated waters there are unknown In the United States at least 400 areas[59] are involved with a majority lying west of the Mississippi River and with Texas being the outstanding individual state involved

Essentially, endemic dental fluorosis is a lifelong disease of the permanent teeth with origin in childhood and before the seventh year of age The deciduous teeth are seldom damaged nor is dental prophylaxis by fluorination of deciduous teeth of proved benefit The milk from nursing mothers is believed to contain insufficient fluorine to produce damage in the deciduous teeth A prenatal influence has been mentioned but not emphasized The occurrence of dental fluorosis originating de novo in industrially exposed workers has not been well substantiated

Pathology — The pathology of dental fluoride osteosclerosis centers about defective calcification of both enamel and dentine but particularly the enamel The enamel rods and inner cementing substance of the enamel are affected eventuating in poor calcification in the tooth crown The involved areas are opaque, while normal enamel is translucent The difference macroscopically may be compared to the opacity of snow ice versus clear ice The damage in enamel later takes on various colors or stains usually brownish which give rise to the unsightly appearance of the teeth The density of the enamel is modified so that erosion may occur The age at which exposure begins and individual susceptibility, together with the level of exposure usually govern the extent of involvement The late molars are least likely to acquire damage (Bull)

The original description by Black as abridged by Kempf and McKay[91] warrants quotation

> The most essential injury occurring in this mottled enamel is the appearance of the teeth The teeth are of normal form but not of normal color When not stained brown or yellow they are a ghastly opaque white that comes prominently into notice whenever the lips are opened In many cases the teeth appear absolutely black Mottled enamel is distinguished especially by the absence of cementing substance between the enamel rods in the outer fourth more or less, of the enamel presenting great variety of color rendering it totally different from anything else I have known

Much speculation has attended the limitation of the hyperplasia to teeth under the circumstances that give rise to mottled enamel while in industrial fluorosis various bony tissues and ligaments may be involved in the absence of dental fluorosis The answer appears to derive from the assumed fact that dental enamel in its formative period is a highly susceptible tissue but after maturity is less responsive and less accessib - to the action of fluoride

The minimum exposure level at which damage may arise is mcr Undoubtedly there exists no precise critical point Dean[6] thus appra the situation

- 1 0 part per million The odds are that the teeth of 1 child in 1(will be damaged all very mildly
- 1 7 or 1 8 parts 1 in 2 affected all mildly or very mildly
- 2 5 parts 3 or 4 out of 5 affected and 1 in 4 or 5 moderately c severely
- 4 parts Almost all children affected and 1 in 3 moderately c severely

The odds increase with higher fluorine content

The well established dental onslaughts of fluorine have led to divers enterprises to abate the exposure In part these efforts run to the abandonment of deep and artesian wells which supply water with unwanted fluorine content and resort to surface waters made safely potable through the usual procedures of filtration chlorination etc and through the precipitation of dissolved fluorides

Elvove[64] in a publication devoted to the removal of fluoride from water observes that tricalcium phosphate magnesium oxide and magnesium hydroxide may be utilized in the defluorination Magnesium

oxide probably is the least expensive So far, costs for defluorination are high

Fluoride Dental Prophylaxis — Fluorine is both bane and boon Increasingly it is becoming established that fluorides at levels incapable of inducing mottling beneficently serve in fending dental caries Apparently some degree of life long protection is afforded when during early childhood teeth are subjected to just the proper amount of fluorides Inconclusive evidence suggests that a lesser degree of protection may be provided adults, but for the time being that issue is here evaded[40]

Over a period of years it has become well determined that in discrete areas in which the drinking water supplies were higher than usual in fluorides but below that level leading to mottled teeth the incidence of carious teeth among long residents chiefly those with childhood resistance is substantially lower This has led to many publications[41] Seeking this benefit numerous cities and villages are regularly treating public water supplies with fluorides and at about 1 p p m concentration

To some extent physicians and dentists are providing fluoride solutions for mouth wash purposes Since fluorides are highly poisonous this practice may be questioned since young children hardly may be trusted with so dangerous a substance Wider spread is the dental practice of painting in the dentist s chair all teeth for several times at intervals with fluoride solutions The Maryland State Department of Health s 1948 appraisal of the situation is consonant with the best current thought

> While there are several aspects to fluoride therapy as a deterrent of dental decay the method accepted and endorsed by dental health authorities is the topical application of a 2 per cent fluoride solution to children s teeth by a trained and licensed dentist Since the technique of application is of the utmost importance it should be administered only by those trained in the science of dental health
>
> Fluoride therapy is *not* a panacea It does not promise to prevent all future decay but only to reduce probable future decay by about 40 per cent on the average Although this reduction is of tremendous importance making it extremely worthwhile to obtain this prevention parents should not ignore the average 60 per cent of decay that will continue to develop Early detection and filling of these cavities by the family dentist remains an important factor in the maintenance of dental health Corrective care by the dentist is also necessary for decay that has started prior to the application of fluoride

Topical application of fluoride must be repeated annually or at least every two or three years if newly erupting permanent teeth are to receive the protection It is now known that the greatest benefits are to be obtained by application to children There is also some evidence that benefit possibly of lesser degree may be had by adults[60]

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oxide probably is the least expensive So far, costs for defluorination are high

Fluoride Dental Prophylaxis —Fluorine is both bane and boon Increasingly, it is becoming established that fluorides, at levels incapable of inducing mottling, beneficently serve in fending dental caries Apparently some degree of life-long protection is afforded when during early childhood teeth are subjected to just the proper amount of fluorides Inconclusive evidence suggests that a lesser degree of protection may be provided adults, but for the time being that issue is here evaded[40]

Over a period of years it has become well determined that in discrete areas in which the drinking water supplies were higher than usual in fluorides but below that level leading to mottled teeth the incidence of carious teeth among long residents chiefly those with childhood resistance, is substantially lower This has led to many publications[94] Seeking this benefit numerous cities and villages are regularly treating public water supplies with fluorides and at about 1 p p m concentration

To some extent physicians and dentists are providing fluoride solutions for mouth wash purposes Since fluorides are highly poisonous, this practice may be questioned, since young children hardly may be trusted with so dangerous a substance Wider spread is the dental practice of painting in the dentist s chair all teeth for several times at intervals with fluoride solutions The Maryland State Department of Health s 1948 appraisal of the situation is consonant with the best current thought

> While there are several aspects to fluoride therapy as a deterrent of dental decay the method accepted and endorsed by dental health authorities is the topical application of a 2 per cent fluoride solution to children s teeth by a trained and licensed dentist Since the technique of application is of the utmost importance it should be administered only by those trained in the science of dental health
>
> Fluoride therapy is *not* a panacea It does not promise to prevent all future decay but only to reduce probable future decay by about 40 per cent on the average Although this reduction is of tremendous importance making it extremely worthwhile to obtain this prevention parents should not ignore the average 60 per cent of decay that will continue to develop Early detection and filling of these cavities by the family dentist remains an important factor in the maintenance of dental health Corrective care by the dentist is also necessary for decay that has started prior to the application of fluoride

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V

ARC WELDING

By CAREY P McCORD

A foregoing section is devoted to the oxides of nitrogen In turn that section is associated with the presentation of the nitrogen acids For the purposes of identifying mineral acids and their precursors with practical and common trade practices, arc welding has been chosen for limited portrayal Instead of this example any one or more of the numerous occupations appearing on the lists of trades utilizing mineral acids such as plating or etching might have been selected

A score or more of peculiar types of welding are applied in industry but all fall into one of the following basic varieties, (1) resistance welding—spot welding, (2) gas welding, (3) thermit welding (4) arc welding All of these forms of welding are attended by divers exposures but arc welding is particularly burdened with hazards some of which stem from the action of mineral acid anhydrides For the purposes of a fair degree of completion all of the significant exposures of arc welding will be mentioned but little further reference to other forms of welding will appear

In arc welding but unwanted and by accident a minor degree of nitrogen fixation occurs in the process of metal union brought about by the high temperatures of the electrical arc The initial current system ordinarily utilizes 440 volts of direct current but in the secondary current the electrical output approximates 31 volts 200 to 225 amps At times bare metal electrodes furnish the onlaid metal but frequently resort is made to coated electrodes The purpose of coating on the electrode is to furnish a gaseous cloud to shield the arc against extraneous gases and otherwise flux the metal The nature of the coating is protean varying from simple lime washes of bare rods through endless combinations of mineral and metal salts to the inclusion of organic, readily combustible additives

The dangers attending arc welding are extensively influenced by special arrangement Inquiry into arc welding disasters more often than not disclose that the welding had been carried out in close quarters Under such conditions anoxia from oxygen deficiency rather than the presence of any precise damaging agent accounts for some disasters

Welding injuries apart from electrical effects seldom arise from weld ing conducted in open areas

With this background it now becomes opportune to enumerate some of the commoner specific exposures linked to arc welding The number embraces ultra violet emanations from the arc distinctly calling for eye protection and skin protection with heavy garments which in turn and at once introduces the malinfluences of accumulated heat around the body The metal of ordinary bare rods is essentially ferrous but on occasion and particularly from welding in small spaces benign pneumoconiosis siderosis (Sander s disease) may appear Although the majority of coated welding rods represent harmless constituents still the number providing possible opportunity for injury is too large for listing

The constituency of the metal being welded may contribute to the hazards run by the welder Should the steel alloy involve a significant content of manganese or lead manifestly some risk may be entailed More importance may be attached to the metal or other coating If the surface represents galvanizing the prospect of metal fume fever from zinc arises If plated with cadmium the evolvement of cadmium fume may provide a direful situation Instead of welding the same equipment may be directed to metal cutting such as in the demolition of bridges or naval craft When applied to metal structures previously coated with lead paints lead poisoning is invited and occurs with distressing fre quency

The gases evolved in arc welding regularly or irregularly are numer ous Literature furnishes many reports alleging deaths from carbon monoxide or carbon dioxide Granting the possibility many such reports represent only unsupported opinions In the electric arc some ozone is always produced but the quantity seldom exceeds five parts per million in proximity to the arc This concentration if breathed might be damaging but such concentration is unlikely to reach the welder even though he be only 24 to 36 inches away The oxides of nitrogen always are present In other than confined work spaces arc welding seldom eventuates in more than 100 p p m of mixed oxides in the breathing zone of the welder As recorded in a previous section devoted to the oxides of nitrogen that concentration might be harmful and the standards there cited are much lower Just what oxides of nitrogen out of the possible five may appear is somewhat unpredictable Equally unpredictable is what may happen to these oxides under some circumstances They may reach the state of nitric or nitrous acid Other circumstances may lead to harmful nitriles and related compounds In

this uncertainty it becomes necessary to be governed by the most unpromising prospect

The symptoms nature of pathological lesion standards and treatment for nitrogen oxide injury such as may afflict arc welders, already have been presented in a foregoing section The occurrence of such abnormal states among welders calls for no procedures dissimilar to those applicable to the same condition from other exposures

From all the foregoing it might be concluded that the perils of arc welding are so great that no welder may hope long to escape the ravages of his multiple potentially damaging agents Actually the situation is otherwise With the exception of ultra violet ray damage against which some protection is an absolute requirement and from the effects of excessive heat welders provide no medical experience that readily sets them apart from other industrial workers involving the same expenditure of energy The frequency of pneumonia is not known to be distinctly higher The gases and other irritants mentioned do not predispose to pulmonary tuberculosis or accelerate that disease In a single large industrial organization fifteen or twenty thousand arc welders regularly employed present no unusual clinical situations From such a welding population most industrial physicians responsible for their care yet have to see their first case of significant pulmonary or respiratory tract edema attributable to oxides of nitrogen However, epidemics of lead poisoning and instances of metal fume fever from arc welding are more frequent From long experience justification appears to attend the statement that most of the disasters to human beings from arc welding arise in petty shops and among little experienced welders An exception to that statement is that in ship building the small space within which arc welding may be carried out may lead to a distinctly higher frequency of all manner of welder s affections Since there is no one characteristic welders occupational disease and dissimilar exposures are numerous diagnostic acumen must be exercised by physicians serving the welding industries

The total published record of arc welding hazards is voluminous Any review will reveal a high number of accidents with fatalities apparently controverting the less alarming experience of the present writer However a critical review discloses that the majority of fatalities occurred from welding under peculiar circumstances, employing unusual work material or welding on unusual metals It is well recognized that departures from good welding practice may be productive of disaster

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VI XXV

METALS

VI

ALUMINUM

By LUDWIG TELEKY

Although aluminum compounds (alumina or argillaceous earth) form 7 to 8 per cent of the earth s crust metallic aluminum was not produced by Wohler until 1828 In 1856 it stood first in commerce The world production in 1913 was 68 200 metric tons in 1938 it was 580 000 and it reached a high point in 1943 with 1 926 000 tons

The most important compounds are the pure aluminum oxide (Al_2O_3) the name of which alumina sometimes caused confusion in the literature It appears in nature is korundum occasionally in the form of ruby (red) or sapphire (blue) but mostly as emery We also find it in bauxite containing mostly 50 to 60 per cent Al_2O_3 besides SiO_2 (2 to 25 per cent) Fe_2O_3 and others

Even more important are the aluminum silicates kaoline or chinaclay (Al_2O_3 2 SiO_2 2 H_2O) which is the basic material of porcelain the other clays providing the material for the pottery and brick industries But we have no intention of discussing these industries here We will confine ourselves to metallic aluminum and aluminum oxide

Metallic Aluminum – The following may be anticipated

In industry there are aluminum alloys much used splinters of which entering the skin very often cause inflammation or subcutaneous swelling sometimes creating a disability lasting 10 to 14 days and even longer These symptoms are caused by the generation of bubbles of hydrogen gas in the tissues It is the magnesium making up only 0 2 to 0 8 per cent of the alloy which brings about this reaction Aluminum itself making up to 95 per cent of the alloy never produces gas bubbles or inflammation in the tissues

What is the effect of aluminum dust inhaled into the lungs? There is a marvellous contrast between observation in former times and those

of today Koelsch and Lederer[1] in 1934 in an aluminum stamp mill, reducing aluminum folies to powder, found no lung changes but a slight chronic irritation of the upper respiratory tract There were 150 particles of dust below 5μ diameter in the cm[3] of air Filipo 1943 reported besides damages in the upper respiratory tract a little increased fibrosis of the lungs of workers in an aluminum stamp mill

First Doese[3] reported in 1938 marked lung changes, small honeycombed shadows in the x-ray picture of a spray painter using aluminum paints for half a year, 16 other workers, less exposed, showed nothing pathological

Goralewski[4] published in 1939 a case history of two workers in a stamping mill exposed to large amounts of aluminum dust besides to copper dust Both had suddenly fallen ill with heavy dyspnea, caused by the development of a spontaneous pneumothorax The x rays showed especially in the middle fields small to medium sized spot shadows In observation over a period of some months no sign of tuberculosis could be found Two additional such cases, one of which also had pneumothorax, published by the same author in 1941[5], showed that the workers had an exposure of 1½, 3, 7, 16 years One of these men, and five others killed by an accident were autopsied by Kahlau[6] He writes The characteristic changes in the respiratory parenchyma is a thickening simultaneously with hyaline transformation When thickened in the highest degree, the alveoles are narrowed to small glandular like formations or even completely obliterated resulting in the focus of a callous hyaline tissue" The greatest mass of aluminum dust lay intracellular in form of finest granules, the greatest part of dust cells lies mostly intra alveolar

R and F Jaeger studied the chemical reactions "In the lungs the aluminum dust comes in contact with the tissue fluids containing NaCl So the reaction aluminum aluminum ion arises, and therefore compounds develop which have an albumin precipitating and tanning effect Besides that, products of this reaction are formed which cause the albumin to swell and to be taken up' This continuous reaction explains the often very rapid progress of the lung changes In animal experiments also lung changes have been produced by inhaling aluminum dust

The statements published concerning this illness induced serial examinations Of 141 workers still active in 8 shops Koelsch[9] found 31 with slight -3 with distinct radiological lung changes The latter author reports also a case with spontaneous pneumothorax Its autopsy revealed the generation of a diffuse connective tissue-like network but no nodules

The picture is summarized with the words 'interstitial pneumonia with cirrhosis

Goralewski[8] examined later 6 8 workers in several stamping mills In the biggest mill with the most unfavorable working conditions 77 or 61 1 per cent of the 126 workers showed the specific lung changes in the other mills 22 2 to 23 2 per cent He describes the x ray picture as fine retiforme increase of the design In this network fine weak not sharply limited shadow touches are deposited which gradually flow together and so make them the impression of homogeneous or cloudy, striped shadows There are also changes in the diaphragm and the heart-shadow and finally gross distortions of the heart outline

Why have these damages by aluminum dust been found now but never in former decades? The principle cause is surely that the aluminum powder produced today is much finer than in former times Then it was greased with stearin now it is greased with vaselin or not greased at all The circumstances of war production caused machinery to be more abused and therefore gave rise to more dusting Also there was less ventilation in consequence of blackout precautions

As astonishing as the appearance of lung damages in the aluminum powder industry is that of nearly identical lung diseases in the production of *corundum*, also performed without similar damages for decades Corundum Al_2O_3 is produced by melting bauxite containing 50 to 60 per cent Al_2O_3 or calcined alumina with up to 98 per cent Al_2O_3 together with a small amount of coal and iron in an electric furnace with a temperature of almost 2 035 C

The detection of lung damages among these workers occurred at the same time in Canada and Germany The Canadians C G Shaver and A R Ridell[10] observed in the years 1942 1946 7 fatal cases after a work time of 31 months to 5 years Examining 344 workers they found 23 well established cases 12 early cases and 13 doubtful cases of lung changes There were 9 cases of pneumothorax among 23 cases referred to in a table

Watjen[11] published the case history with lung and autopsy findings of a corundum melter who died in 1944 J Hagen[1] reported in 1948 about a corundum melting plant In former times occupational lung damages were never reported to him as the medical inspector of factories But since 1945 23 cases have been reported among them 9 fatal cases 5 of which came to autopsy The clinical and the autopsy pictures were in complete agreement with those described by Goralewski[8] Watjen[11] and Shaver and Ridell[10] the sudden onset of symptoms the

formation of pneumothorax The x-ray pictures showed opacities coarser shadows Microscopically reticulate fibrous shadows were seen but never sharply demarcated as silicotic nodules are The densities often reminded one of ramificated pneumonic focusses'

Jephcott and colleagues examined in the Canadian plants the production of fumes and other working conditions to which furnace workers were exposed Dust counting could not be achieved in a fully reliable way because the single particles are partly too small to be seen under a microscope being on the order of a few hundredths of a micron The counts including only those particles which are greater than about one quarter of a micron in diameter, showed large variations Those taken with the impinger showed 393 to 1,085 particles per cubic centimeter The chemical analyses of the fumes showed 28 93 to 44 24 per cent SiO_2 40 69 to 62 15 per cent Al_2O_3, about 3 to 4 per cent Fe_2O_3 and 1 to 2 79 per cent MgO The fumes consisted chiefly of very finely divided amorphous alumina and silica The lung ash contained 29 0 to 40 4 per cent Al_2O_3 and 21 0 to 30 5 per cent silica, which shows that an appreciable amount of fume is retained by the lung

The authors state that although these processes were performed in Canada from 1914 the lung changes have only recently been noted They think that the increased production with the high concentration of fumes was probably the main factor in the causation of the lung changes The fact must be emphasized that only furnace workers have been affected and no other workers in the plant In grinding shops using corundum wheels no other lung changes have been seen except, after decades of work a slightly increased fibrosis

This is certain, we see serious characteristic and approximately identical lung changes caused as well by aluminium oxide (in combination with SiO_2) as by metallic aluminum dust

On the other hand there have been extensive researches and practical attempts made to use *aluminum dust as a prophylactic therapeutic against silicosis* The Canadians J J Denny, W D Robson and D A Irwin[14] demonstrated by careful researches of long duration, first in vitro that the solubility of quartz in water is increased by certain materials and decreased by others It is decreased by many compounds of aluminum ($Al(OH)_3$ Al_2O_3 Al_2U_3 Ba (Bauxite)), but their result is less satisfying than that given by metallic aluminum Rabbits which inhaled silica dust with an addition of aluminum (less than 1 per cent) or one kind of dust after the other, developed no silicosis as occurred in those inhaling quartz dust alone Further research[15] showed that the "metallic

aluminum on being converted into hydrated alumina reduces the toxicity of quartz in three ways, a) by flocculation b) by absorbing silica from solution but c) chiefly by coating the quartz particle with an insoluble and impermeable coating' 'This coating has been definitely identified as a gelatinous hydrated aluminum which on drying forms the crystalline alpha aluminum monohydrate boehmite $(Al_2O_3H_2O)$' In the animal experiments also it had been demonstrated that aluminum dust even inhaled for a long time in great amounts does no harm either to the lung or to the general health

L U Gardner and associates[16] performing animal experiments amply verified the facts found by the Canadians but they suggest that amorphous hydrate of alumina may possess certain advantages over the metallic aluminum Their work showed however that excessive concentrations of aluminum hydrate may influence unfavorably native susceptibility to tuberculosis Therefore it would be unwise to use it in cases showing x ray evidence of any but the oldest and obviously well healed tuberculous lesions Gardner and associates went even a step further They tried to determine whether existing silicious changes may be altered by introduction of aluminum They found this treatment surprisingly effective Hydrated alumina inhalation as a treatment for disease that is already established has been shown to cause retrogression of immatures silicotic lesions its only effect upon fully developed fibrous nodules is to prevent their further enlargement In silicotic animals treatment prolongs life and in men with disability it is said to relieve dyspnoea cough and chest pain * * * In conclusion it may be said that confirmed experimental evidence proves beyond question that aluminum and aluminum hydrate probably in amorphous state specifically inhibit fibrous reaction to quartz and that their administration will prevent progression of silicotic lesions and cause retrogression in immature tissue responses"

In a newest publication E J King and colleagues wrote "Nodular reticulosis was present in the lungs of quartz dusted rats from about the two hundredth day and fully developed collagenous silicosis from about the three hundredth day The quartz plus aluminium ([illegible] per cent of metallic aluminium powder in the quartz) dusted rats had almost no reticulosis in their lungs at two hundred days and only very slight reticulosis at three hundred days

To summarize the results of the excellent research and animal experiments performed as well by the Canadians as by Gardner and his collaborators and King and his colleagues (other authors contributed very

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little to these questions except those who tried to use it in practice) we have to state that a preventive effect of aluminum against development of silicosis seems fairly well stated, and the principal question may be to transfer effectively to human beings the method that has been used on animals Much less well founded is the use of aluminum as therapy, the effects of which has certain borderlines created by the impossibility of altering the fibrotic silicious changes, here is shown the possibility only of preventing further silicotic developments That is a kind of therapy which is very near to prevention or perhaps is prevention

Therefore we will discuss first the experiments with *prevention* There have been attempts to mix the quartz dust immediately in the place of its generation in the mine itself That proved very difficult (Jacob[1]) Therefore and because it had been shown that the effect is the same whether mixed dust is inhaled or both separately at different times another way has been elaborated and is in use In a special apparatus freshly generated aluminum powder* is produced This powder looks like lampblack every particle has a kernel of metallic aluminum being 20 per cent surrounded by 80 per cent aluminum oxide In the change house while the men are donning their underground clothes before entering the shaft such aluminum dust is dispersed by a special apparatus in such a way that one gram of aluminum dust covers one each 28 cubic meters of the room when the workers *stay in the room for 10 minutes, when the time is 20 minutes* then half that amount That corresponds to 30,000 to 35 000 particles in a cubic centimeter, 90 per cent of the particles have a diameter up to 1μ, 99 per cent below 5μ The first investigations were undertaken at the McIntyre Porcupine Mines Schunmacher Ontario A McIntyre Research Ltd has been founded as a non profit undertaking Patients have been taken out on the apparatus and the material For one dollar per man yearly licenses are given to dust plants but under certain conditions only concerning accomplishment and medical supervision The McIntyre Research Ltd itself supervises the carrying out of the requirements and the results It hopes to hinder in this way irrational use of the method and to clarify the question of its effectiveness This surely may succeed if the Research Ltd appoints intelligent supervisors It is sure that years are necessary to ascertain clearly the efficiency of this prevention

* It may be mentioned that there is on the market another aluminum powder produced from aluminum foils platelets with 5 to 10 diameter which cannot be used for inhalation experiments because it does not penetrate into the lung alveoli

It should be mentioned that all the authors correctly stress that other methods of prevention the engineering ones good ventilation exhaust devices wet drilling should in no way be neglected

Therapeutic effects have been published already The first experiments were made by Crombie[18] The treated workers had a clear silicosis without tuberculosis were under 55 years of age had worked in the mine at least 5 years were not more than two years out of work and showed definite disability recognized by the workmens' compensation board The inhalation apparatus was so arranged that the patient received about 1 mgm aluminum dust per minute The time of treatment was first 5 minutes increased in a few days by 5 minutes up to 30 minutes The treatment was given six days weekly up to 200 and in some cases 300 treatments The results may be seen in Table I as well as in other reports published just recently Gardner and Wright treated five serious cases with metallic aluminum two with hydrated aluminum in the same way and gave about the same number of treatments The following authors Johns and associates[19] Bamberger[20] treated much slighter cases and gave only 30 to 40 usually 30 treatments with about the same results Another author Hanon[21] alone reports excellent results after 40 to 60 treatments each for a shorter time i e using about the tenth part of the aluminum as used by Crombie for every case His results were excellent Such differences between the last and the former surely reliable authors can be explained only by an entirely different and not so exact kind of evaluation of the latest We hope that reliable observations may be published soon based on more extensive material

The Council on Industrial Health and the Council on Pharmacy and Chemistry of the American Medical Association in 1949 came to this conclusion

1 Studies on the therapy of silicosis thus far have been inadequately controlled The majority of subjects have reported subjective improvement apparently of psychic origin No convincing evidence of objective improvement either of pulmonary function or by roentgen ray has been forthcoming Certain cases have shown eventual progression by roentgen ray subsequent to aluminum therapy under present conditions of dosage

2 It is too early to expect evidence of the effectiveness of aluminum prophylaxis in men who do not have a history of exposure to silica dust prior to the beginning of the therapy and prophylaxis of silicosis Whether or not it increases susceptibility to tuberculosis is unproved

TABLE I

	Improved	Slightly Improved	No Changes	Deteriorated
Crombie and associates[18]	7	12	15	—
Gardner and Wright[17]	2	—	5	—
Johns and Petronella[19]	3	19*	21	—
Bamberger [0]	24	—	0	5
J W G Hanon[21]				
workers selected	33	—	—	—
workers with x ray changes and disability	135	—	6	2
workers with x ray changes denying disability	93	—	11	—
ceramic workers[2] with moderate to severe disability	36	—	10	—
I W Berry [3]	3	—	15	8

No findings in history or physical examination stating that they feel better as far as general health

However great care should be taken to exclude the tuberculous in selecting persons to receive aluminum therapy Research should be continued'

Since that time there are no reports of experiences with man in this field

Summarizing we may say About no other metal, except perhaps beryllium have the experiences of the last decade brought such astonishing statements, partly in contradiction to former observations There can be no doubt that the statements concerning the diseases in aluminum and corundum plants are correct as are the results of the research work done by Denny and Gardner and their collaborators, but further practical experiences are necessary to evaluate the effect of aluminum as a therapeutic and prophylactic

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workers selected	33	—	—	—
workers with x ray changes and disability	135	—	6	2
workers with x ray changes denying disability	93	—	11	—
ceramic workers with moderate to severe disability	36	—	10	—
I W Berry[23]	3	—	15	8

No findings in history or physical examination stating that they feel better as far as general health

However great care should be taken to exclude the tuberculous in selecting persons to receive aluminum therapy Research should be continued"

Since that time there are no reports of experiences with man in this field

Summarizing we may say About no other metal, except perhaps beryllium, have the experiences of the last decade brought such astonishing statements partly in contradiction to former observations There can be no doubt that the statements concerning the diseases in aluminum and corundum plants are correct as are the results of the research work done by Denny and Gardner and their collaborators, but further practical experiences are necessary to evaluate the effect of aluminum as a therapeutic and prophylactic

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VII

ANTIMONY

By RONALD F BUCHAN

Industrial exposure to antimony occurs in mining the ore smelting and refining it, also in processes where it is alloyed with other metals commonly copper, lead or tin Such alloys are utilized in pipe metal pewter storage battery grids, metal bearings and printers type It is used also in the manufacture of munitions It will be noted that exposure to antimony usually involves multiple metallic exposures

There have been few cases of occupational antimony poisoning reported in the American literature From German experience[1] comes observation on a number of workers in a pipe foundry who had remarkable facial expressions fatigue loss of appetite nausea gastrointestinal disturbance and constipation, nervousness sleeplessness irritability dizziness muscular and neuralgic pains This symptomatology it will be noted seems to be a combination of the gastrointestinal and central nervous system reactions common to many metal poisonings From the German experience such cases have a concomitant diminished leukocyte count and eosinophilia of considerable degree Habecl discussing the findings of Boader Schrumpf and Zabel[1] and Seitz emphasizes the presence of leukopenia in all three studies Feil[3] states that half the workers in his study had anemia and on exposure to antimony vapors developed rashes and pustules similar to smallpox of the neck forearms and legs Other common complaints were anorexia headache and conjunctivitis

The American experience is quite meagre Animal experimentation has revealed an extensive degree of pathology involving the lungs liver lymphatic system and hematopoietic system which is not duplicated in the clinical cases on record Bradley and Frederick[4] citing animal experiments declare that the most consistent finding is injury to the myocardium regardless of the compound or dose They suggest routine EKG studies on workers with occupational exposure to antimony

Dernehl Nau and Sweets[5] on the contrary in a series of guinea pig experiments detected no abnormalities in electrocardiograms of exposed animals Schwartz and associates[6] say that the inhalation of metallic antimony dust is productive of diarrhea in some workers They also

17 JACOB A W The engineering aspects of aluminum prophylaxis Canadian Mining and Metallurgic Bull, 1944 XLVII, 185
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system symptoms and physical examination directed toward elicitation of any significant signs in these systems with careful scrutiny of the skin and mucous membranes is indicated

Therapy is local and symptomatic depending upon the reaction present and its severity The patient should be removed from exposure Skin lesions usually are best left alone except for implementation of cleanliness Scarring can be expected from the nature of the lesion Stibine intoxication is a medical emergency Attention must be directed to the hemolytic phenomena and calls for prompt administration of whole blood oxygen and intravenous glucose Continuing supportive therapy will include ferrous sulfate during the regeneration of the peripheral blood picture While there have been few reported cases of antimony poisoning it would seem that the experience of industry is not inconsiderable and further careful epidemiological investigation should enhance our present knowledge in significant degree

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7 FAIRHALL L T and HYSLOP F The toxicology of antimony Pub Health Rep Suppl No 195 1947

8 HAMILTON A and HARDY H L Antimony in Industrial Toxi cology pp 159 Paul B Hoeber Inc New York 1949

9 BULMER F M R and JOHNSTON J H Antimony trisulphide Jour Indust Hyg and Toxicol 30 XXVI 1948

quote Oliver and Meyer and Gattbil who observed pustular lesions similar to those described by Feil It is stated that the antimony causes the pustular lesion by necrosis of the cells Schwartz and associates[6] observed ulceration of the nasal septum attributed to the dust of antimony trichloride and report keratitis following exposure to the dust and fumes Gastrointestinal distress, irritation of the mucous membranes and skin reactions particularly a pustular eruption resembling in many instances the lesions of smallpox, are the most commonly reported reactions to antimony and its compounds The dermatological manifestations from compounds of antimony are not rare and seem to be in their pustular variety a rather characteristic phenomenon, arising from contact with antimony trichloride, trioxide, pentasulfide and tartrate Fairhall[7] attaching more than average significance to the toxicity of metallic antimony and its salts grades them in descending order of toxicity as metallic antimony, trisulphide, pentasulphide, trioxide and pentoxide

Clinical experience has not followed experimental or theoretical concepts with any consistency Hamilton's[8] experience with workers coloring rubber goods and exposed to antimony sulphides was productive of no clinical evidence of damage Bulmer and Johnston[9] are in accord with their more recent reports on exposure to antimony and its salts

Stibine the hydride of antimony (SbH_3), arises under conditions not infrequently met with in industry Commonly nascent hydrogen in contact with metallic antimony or a soluble compound will produce the colorless, offensive gas Such conditions are encountered in the manufacture of storage batteries Water in contact with hot antimony containing alloys may evolve stibine as will acid treatment and electrolytic action of antimony compounds

Similar to arsine in properties and toxicity, it is nevertheless less stable than arsine and with an undefined incidence of morbidity Generally encountered in a mixture of other poisonous gases, Nau and colleagues[10] and Dernehl and co workers[11] report possible examples of stibine intoxication Because of its use in alloys and in combination or in conjunction with other toxic materials it is necessary to weigh carefully the evidence and investigate thoroughly the possibility of other toxic exposures when considering antimony as a source of industrial poisoning

Prevention is dependent upon proper engineering control with associated medical control Inquiry into gastrointestinal and central nervous

VIII

ARSENIC

By RONALD F BUCHAN

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Arsenic finds a wide variety of uses in industry The so called red arsenic arsenic disulfide is utilized in paint and varnish pigments in dyeing textiles and in the preparation of pyrotechnic products Arsenic trichloride an oily liquid is used in the manufacture of ceramics and certain drugs So called white arsenic arsenious acid, arsenious oxide arsenious anhydride arsenic trioxide is an ubiquitous compound and is found commonly in the manufacture of arsenic acid aniline dyes ceramic enamels fly paper fungicides rodenticides parasiticides boiler compounds various pigments particularly pinks greens browns and blues medicinal soaps as a mordant in dyeing for coloring metals and for certain therapeutic uses

Arsenic is also a common contaminant of the ores of other metals As a constituent of sulphide ores arsenic will constitute a hazard in the extraction of lead iron copper antimony and zinc from their sulphide ores

In general toxic occupational exposures arise from contact with dust of solid compounds from cutaneous absorption of arsenic trichloride following spills and from the gas arsine Acute intoxication is seen upon exposure to hydrogen arsenide or arsine a gas and to absorption of arsenic trichloride through the skin Arsine is not used in industry Exposure to it arises accidentally However because of the ubiquitous nature of arsenic there are numerous possibilities for the formation of arsine which occur when metals containing arsenic as an impurity come in contact with sulfuric or hydrochloric acid

10 NAU C A, ANDERSON, W and CONE R E Arsine, stibine and hydrogen sulfide Accidental industrial poisoning by a mixture Indust Med 308 XIII 1944
11 DERNEHL C U STEAD F M and NAU, C A Arsine stibine and hydrogen sulfide Accidental generation in a metal refinery Indust Med, 361, XIII, 1944

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as may be noted in the form of keratoses of the palms and soles Indeed the whole question of arsenic keratogenesis and neoplasia is one surrounded with numerous circumstantial and as many objective observations In this regard it would seem safe to say that the only three unquestionable etiological agents in human cancer[4] are arsenic beta-napthylamine and radiation and of these only the latter two have been definitely associated with occupational cancer Consequently a brief consideration of arsenic and neoplasia is indicated

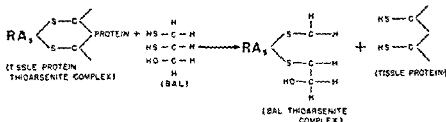
Neoplasia — Melanosis and hyperkeratosis due to chronic intake of Fowler s solution have been long recognized Dermatological malignancies arising in such lesions have been noted The Reichenstein[4] cases associated with arsenic polluted drinking water have every indication of authenticity Consequently a high index of suspicion exists among physicians when evaluating occupational hazards associated with arsenic exposures However the epidemiology of such classic alleged arsenic cases as the lung cancers of Schneeberg and the skin malignancies of shale oil workers has not survived the scrutiny of objective and scientific appraisal Animal experimentation[5, 6] has tended to exclude arsenic as an external source of skin cancer Cases of keratoses and epitheliomata attributed to occupational arsenical exposure with subsequent development of malignant changes have been reported[7] but age outdoor exposure and other factors are not objectively evaluated Hueper[8] discussing the diagnosis of arsenical epitheliomata emphasizes the importance of the following diagnostic criteria 1 positive history of exposure to arsenic 2 clinical demonstration of cutaneous manifestations characteristic of arsenico-dermia 3 histochemical demonstration of arsenic in the skin 4 demonstration of arsenic in the hair and urine

Salter[3] however in analyzing the arsenic content of cutaneous neoplasms of the hand and external ear arising in a case of human hyperkeratosis due to potassium arsenite found no difference in the hyperkeratotic or neoplastic tissues as compared with any normal skin Schwartz and associates[9] state that no records of occupational cancer attributable to arsenic are to be found in the reports of State Compensation Boards Thus while occupational keratoses have been rather commonly observed and cutaneous neoplasms due to chronic intake of arsenical medications or arsenic contaminated water supplies have substantial basis no significant deposit of evidence exists to incriminate arsenic as an external carcinogenic agent in occupational exposures Ulceration of the skin and nasal septum has been reported[10] commonly among arsenic workers This is a lesion which is also commonly encoun

Arsine is an hemolytic agent Dependent upon the degree of exposure the patient will suffer from nausea, vomiting, gastric pain headache dizziness and anoxemia In a period of a few hours up to a day or two following exposure the urine will become dark red or burgundy color Albumin and casts appear in the urine Following shortly upon the hemoglobinuria there is an hematogenous jaundice with pain, tenderness and swelling of the liver There is a marked diminution in the red cell count and a concomitant, proportionate fall in the hemoglobin In fatal exposures the patient will become anuric with a general bronzing of the skin with a rapid downhill course precipitated by hemorrhagic nephritis and hemorrhagic destruction of the liver The mortality in such exposures is about 30 to 40 per cent For those, who do not become anuric the urine will gradually regain its normal color, although albumin may persist for some period after cessation of the acute symptoms There will be a residual anemia of marked degree responsive to iron therapy Those patients, who do recover, will have no residual disability Exposure to arsenic trichloride or its fumes may result in acute arsenicism with severe gastrointestinal and central nervous system irritation Vomiting, tenesmus and diarrhea lead to dehydration and collapse Prostration and general paralysis may predominate due to the cerebral effects

Postmortem examinations of patients dying from arsine poisoning substantiate the clinical findings in that the greatest damage is due to hemolysis caused by the oxidation of arsine to elementary chloridal arsenic which destroys the red cells Fatty degeneration of the liver is noted, the spleen usually is enlarged soft and dark red The kidneys are dark red with cloudy swelling and intravascular hemolysis and the uriniferous tubules are filled with blood Steel and Feltham[1] give a useful summary of the clinical and pathological literature in reporting a case of arsine poisoning later checked by controlled experiment

Chronic manifestations of industrial origin are ordinarily local and dermatological rarely systemic Butzengeiger[2] however, describes electrocardiographic studies of several hundred wine growers subjected to long term arsenical insecticide exposure The variation from normal incidence is stated to be significant in volume confirmed by rabbit experiment and diminishing in the human subjects during the war years when the arsenical products were unavailable Unfortunately the rabbit protocols were lost in the war There has been no further confirmation of these observations Numerous observers have reported that exposure to arsenic dusts produce dermatitis melanosis and epidermal hyperplasia



Intramuscular injection is the route of BAL administration for systemic intoxication with dosage adjusted to body weight at 5 mgm per kg or 0 0.5 c c per kg This dose should be repeated at four hour intervals for a total of four to six injections on each of the next two days and two injections daily for the next eight days for a total period of ten days or until complete recovery In arsine poisoning the dosage may be stepped up to 5 mgm per kg for the initial dose followed by 5 mgm per kg injections at two to four hour intervals during the first twenty four hours An ophthalmic ointment containing BAL in water soluble base is particularly effective for corneal lesions due to arsenical gases

General supportive measures should be utilized in conjunction with BAL in acute cases arising from arsine or arsenic trichloride Intravenous replacement of fluid whole blood transfusion and oxygen should be utilized in accordance with the indications of the case Ferrous sulfate up to one and one half grams per day may be administered during the period of anemia with due consideration to the usual side effects

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tered in chrome and copper exposures Generalized dermatitis occurs, and vesicular or bullous dermatitis of the lower abdomen groin and thighs has been noted

The mucocutaneous junctions and the skin of the scrotum and axillae seem to be particularly sensitive to arsenical effects Lead arsenate, commonly used as an insecticide, is productive of intoxication related to the lead rather than the arsenic content of the compound, and the lesion usually noted in relation to exposure to this product is that of the peripheral nervous manifestations of lead intoxication Rarely a generalized chronic arsenical poisoning may be noted in industry however it is seldom severe It is manifested by a polyneuritis and motor palsy affecting the long extensors similar to lead and is said to be distinguishable from the latter by neuralgic pains Legge[11], in a review of 135 cases enumerated the following symptoms, gastric symptoms—38 tremors or muscular cramps—13, peripheral neuritis—6, the remainder all had lesions of the skin, 6 of whom had keratoses or epitheliomata

Prevention of industrial intoxications from arsenic should be directed toward the causes of chronic and acute manifestations Chronic manifestations arising from exposure to dust, essentially dermatological in nature may be prevented by proper engineering control methods to reduce the volume of emanated dust Workers in addition should give particular attention to personal hygiene with utilization of clean work clothing and daily showers and scrubbings to remove arsenic contaminated soil Periodic medical examinations should direct particular attention to scrutiny of the skin and mucous membranes of the nose throat and pharynx Septal perforations may be prevented by the use of bland ointments or ointment impregnated cotton plugs

Possibility of arsenic poisoning should be recognized in dealing with acids and metals Processes should be properly ventilated to obviate inhalation of any emanated arsine

Attempting to combat the effect of arsenical gases British scientists during the war synthesized 2, 3 dimethylmercapto propanol generally known as BAL (British Anti Lewisite) It is believed that the toxic effect of arsenicals are due to the combination of the arsenicals with sulphydryl groups in the tissues The British investigators attempted to introduce a product which would form a stable ring with the arsenicals obviating the formation of the sulfhydryl group The following diagram illustrates the rationale of BAL therapy

IX

BARIUM

By RONALD F BUCHAN

Barium ordinarily is used industrially as the monosulfide in the manufacture of barium salts hydrogen sulfide gas for coloring copper in rich shades of brown for luminous paint, for weighing gutta percha vulcanizing rubber as a depilatory and as a laboratory reagent Physicians are familiar with the use of barium sulfate for fluoroscopic or roentgen studies Ordinary table salt is commonly contaminated with barium chloride As with any dust particularly one of caustic quality workers exposed to quantities of carbonate sulfide or oxide will complain of mucosal irritation Serious systemic reactions however from barium and its salts are due usually to accidental ingestion of the carbonate or the sulfide when barium sulfate was the intended compound When such is the case ingestion is followed by nausea salivation and great weakness with subsequent vomiting tenesmus and diarrhea The mucous membranes of the respiratory tract and the eye are irritated with catarrhal manifestations Dermatological reactions are noted with exposure to the sulphide and sulphate and are represented by contact eruptions and ulcerations Esser[1] discusses in some detail the toxicology of several metals including barium appending an extensive bibliography which is of particular interest Bertarelli denies the presence of toxic reaction to barium chloride in discussing long periods of occupational exposure Thus industrially barium is not a material of great toxic significance except for accidental ingestion

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ceramic industry has learned to make use of the properties of this remarkable element This detailed list of uses is included to enable the clinician to take a helpful occupational history in the presence of the possibly confusing syndromes which have appeared in the beryllium industry

History of Illness in Beryllium Industry

Records of illness in the beryllium industry date from 1933 when Weber and Engelhart[1] in Germany reported bronchitis and bronchiolitis in workers extracting beryllium from the ore Fabroni in 1935 did animal studies for the Occupational Disease Clinic in Milan Italy, producing what he called berylliosis with beryllium compounds Gelman and his colleagues[3,4] in Moscow presented a comprehensive clinical report of ill effects of beryllium to skin mucous membranes and respiratory tract These observations were made among workers in the extraction process which involves the use of fluoride compounds Gelman held that the effects observed might be due to presence of the fluoride radical in the worker s exposure Berkowitz and Israel[5] in 1940 also writing from Russia described the physical findings of 46 worker patients from the same industry and designated the picture as beryllium fluorine intoxication Meyer[6] (1942) discussed what he felt was a unique pulmonary disease observed in German workers engaged in beryllium extraction involving exposure to beryllium silicates the hydroxide sulphate and chloride of beryllium but not the fluoride Wurm and Ruger[7], colleagues of Meyer presented at the same time pathological studies of the fatal cases in this series and the results of animal studies to establish Meyer s contention that this occupational disease was due to the inhalation of beryllium dust

These European writers in summary describe in varying degrees symptoms of cough and dyspnea x ray pictures easily confused with miliary tuberculosis and at post mortem types of pneumonia variously called carnifying alveolitis and chronic large celled pneumonia

In 1943 Van Ordstrand and associates[8] described a chemical pneumonia occurring in Ohio workers engaged in extracting beryllium from beryllium ore This is the first report from the U S A Shilen and associates[9] in the same year reported respiratory tract disease from the beryllium industry in Pennsylvania assigning the cause to the fluoride compounds Since this time reports have appeared in the medical liter-

X

BERYLLIUM

By HARRIET L HARDY

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Introduction

Beryllium the fourth lightest element with an atomic weight of 9 02, is extracted in varying quantities up to 17 per cent from beryl ore The ore is found in Brazil, Germany, Russia, India and in this country in small amounts in the New England States and the Dakotas Beryllium has enjoyed increasing industrial popularity since the discovery by chemists that alloys with copper aluminum nickel, magnesium silver iron steel are light and highly resistant to heat and stress of any kind In the late 1930 s beryllium was compounded with zinc, manganese and silica to make a phosphor which fluoresced when exposed to ultraviolet light and because of this was used to make fluorescent lamps Because of its property of giving up neutrons, when bombarded by alpha particles beryllium is used in atomic energy development Beryllium and its compounds are or have been, used in varying amounts in the manufacture of luminous indicators, x-ray tube windows, Welsbach mantles, neon sign tubing incandescent lamps electric heating elements, radio and electronic tubes and heat refractory crucibles and bricks The

ceramic industry has learned to make use of the properties of this remarkable element This detailed list of uses is included to enable the clinician to take a helpful occupational history in the presence of the possibly confusing syndromes which have appeared in the beryllium industry

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ature annually Illness has been recorded from the following industries, beryllium extraction manufacture of alloys, manufacture of beryllium-containing phosphors manufacture of fluorescent lamps fluorescent lamp salvage research work involving beryllium compounds on a laboratory scale manufacture of neon sign tubing, x-ray tube window manufacture brass manufacture, radio tube manufacture, silica crystal manufacture ceramics work machining beryllium (see Machle and associates[10], Williams[11] and Aub and Grier[61])

In addition it is now established that a few persons living in close proximity to plants handling relatively large amounts of beryllium have developed illness identical with that seen in workers The Russian writers (Gelman and associates[3, 4]) noted that watchmen 100 meters from any beryllium operation developed symptoms There is now reasonable evidence that workers may carry home enough pathogenic beryllium compound to cause illness in some member of his family These facts make certain beryllium compounds a public health as well as an industrial toxicological problem

Table I summarizing the medical literature demonstrates the many titles that have been used to describe illness in the beryllium industry Since the toxic effects of certain beryllium compounds is clearly indicated by epidemiological evidence it seems proper to use the term beryllium poisoning to cover all clinical syndromes As indicated the modifying terms acute chronic, etc, may be included Beryllhosis is an alternate term but frequently is misused as berylosis' referring to beryl ore which thus far has not been incriminated as causing illness

Pathological Physiology and Pathology

The postmortem study of cases of acute poisoning in the USA reveals according to Goldblatt (see Van Ordstrand and associates[1]) pathological findings in the lungs only He describes the picture as a chemical pneumonitis Plasma cells edema, hemorrhagic extravasation and some organization with fibroblasts were the striking features

The pathology of chronic beryllium poisoning (see Jetter in Hardy and Tabershaw[13] Martland[14] Grier and associates[15] Dutra[16] and MacMahon and Olker[40]) is a granulomatous lesion involving always the lungs and in varying degrees, liver spleen and lymph nodes The histological changes vary with the length of time the patient with the disease lived In a short, violent course many emphysematous blebs accounting

TABLE I

SUMMARY OF LITERATURE

Authors	Date of Publication	Beryllium Compound Mentioned	Diagnosis
1 Weber and Engelhardt[1] (German)	1933	Extraction of Be	Bronchiolitis
2 Fabroni (Italy)	1935	Be carbonate	Berylliosis (animals) Forms of pneumonia
3 Gelman (Russia)[3]	1936	Be metal Be oxyfluoride	Metal fume fever Bronchiolar colitis
4 Berkovits and Izrael (German)	1940	Be metal Be fluoride	Fluorine beryllium vapor intoxication Acute bronchiolitis
5 Meyer (Germany)[6]	1942	Be oxyfluoride Be silicate Be hydroxide	Pulmonary sclerosis Berylliosis Chronic large celled pneumonia
6 VanOrdstrand and Associates (Ohio)[1]	1943	Be sulphate Be chloride Extraction of Be Be oxide	Chemical pneumonia
7 Shilen and Associates (Pa.)[5]	1943	Extraction of Be Be fluoride Be oxide	Respiratory ailments Dermatitis
8 Kress and Crispell (Ill.)[1]	1944	Fluorescent powder Be carbonate Be manganese sulphate	Atypical pneumonitis
9 VanOrdstrand and Associates (Ohio)[3]	1945	Be metal Be oxide Be sulfate Be fluoride Be oxyfluoride	Beryllium poisoning Contact dermatitis Contact conjunctivitis Chemical nasopharyngitis Chemical pneumonitis
10 Hardy and Tabershaw (Mass.)[3]	1946	Fluorescent powder Zn Mn Be silicate	Delayed chemical pneumonitis
11 Koelsch (Germany)	1947	Be silicate Be sulphate Be hydroxide Be chloride	Bronchitis Atypical pneumonitis

Authors	Date of Publication	Beryllium Compound Mentioned	Diagnosis
12 Martland and Associates (New Jersey)[14]	1948	Be O? Be alloys?	Beryllium poisoning
13 Machle and Associates (USA)[10]	1948	Be O Zn Mn Be S O_4	Berylliosis Acute Pneumonitis of beryllium workers and pulmonary granulomatosis of beryllium workers

for the occasional case of clinical spontaneous pneumothorax, and extensive cellular replacement of normal tissue, are seen Following a long clinical course there is extensive granulomatous organization with many giant cells and hyaline fibrosis European reports of illness in the beryllium industry (see especially Wurm and Ruger) present striking similarities to the pathology following experience in this country

Skin lesions arising spontaneously in chronic beryllium poisoning show on microscopic study after biopsy a granulomatous reaction In addition Grier and associates[15] have drawn attention to the fact that a few persons who cut themselves on fluorescent lamps may develop subcutaneous granulomata Spectrographic analysis shows the presence of beryllium and the histopathology is like that of the skin and lung lesions found in worker cases of chronic beryllium poisoning

Biopsy of the liver and lymph node in several cases has demonstrated a variety of cellular reactions which are unique pathologically, and in most instances are seen to belong to the granulomatous reaction considered characteristic of beryllium poisoning Beryllium can be detected in most of such biopsies

Wright[18] of the Trudeau Foundation has established the characteristic pulmonary pathological physiology of chronic beryllium poisoning as oxygen unsaturation because of an obstruction to the passage of that gas across the alveolar membrane In severe cases there is a loss of breathing reserve Bruce and associates and Whittenberger and his associates have corroborated these observations reporting also depressed vital capacity and maximum breathing capacity with an increase in residual air The changes in alveolar arterial oxygen saturation are uniformly reported as the most sensitive indication of disability in residual air

The changes in alveolar arterial oxygen saturation are uniformly reported as the most sensitive indication of disability in chronic beryllium poisoning

Investigation of Beryllium Toxicity

European workers have produced pulmonary lesions with a variety of beryllium compounds (Weber and Engelhardt[1], Fabroni[2], Policard[3] and Davies and Harding[50]). Beryllium rickets[12, 20, 21] so called has been used as a laboratory tool since 1931 when Branion and associates[1] produced bone lesions by putting beryllium carbonate in the diet of rats. Loomis and Bogen[4] in 1935 showed that tubercle bacilli in guinea pigs multiplied faster if beryllium salts were injected. Hyslop and associates[5] of the United States Public Health Service published an exhaustive study of the toxicology of beryllium after reviewing the literature and making animal studies with beryllium compounds. They reported changes in bone and lung but did not believe they had sufficient evidence to incriminate beryllium itself. Gardner of Saranac studied the pathology of beryllium poisoning and began in 1943 extensive animal studies with beryllium compounds from industry where illness had occurred. Gardner reported bone sarcomas with metastases to lung and liver some months after injections of certain beryllium compounds into rabbits. This work has been amply confirmed[34, 55, 56, 43]. Scott[33] showed that chronic intravenous injection of beryllium sulfate produced osteosclerosis in rats. It is interesting that post mortem study of the femur in one case of human chronic beryllium poisoning showed a curious increase in hardness characterized as "like marble bones" of animals.

Hoagland[8] has studied the growth promoting effects of beryllium upon plants and has related this phenomenon to magnesium nutrition on the one hand and specific effects of beryllium upon the phosphatases of these plants on the other hand.

Before his death in 1946 Gardner produced granulomatous lesions in lung, liver and lymph nodes using in animals beryllium compounds incriminated by industrial experience. Vorwald[19] his successor is extending this work at the Saranac Laboratories which Gardner had not published feeling it not sufficiently specific. Acute beryllium poisoning in animals has been reproduced and extensively studied by the Rochester group[11, 4, 41] and Aldridge and associates in England[49].

Crowley and associates[57] using Be^7 the radioactive isotope showed that in small animals tracer doses of Be^7 are distributed to liver, bone and kidney after about one half the dose is excreted promptly in the urine. The beryllium did not leave bone during the length of the experiment.

Of great interest is the work of Grier and associates[51], DuBois and

associates[35] and Klemperer and associates[36], showing that beryllium has an inhibitory effect on alkaline phosphatase It has been suggested further by these workers that beryllium competes successfully with magnesium under experimental conditions

CLINICAL SYNDROMES

Clinical experience is sufficiently great and currently accumulating to enable a classification of the clinical syndromes seen in certain beryllium exposures It is reasonable to describe acute beryllium poisoning and chronic beryllium poisoning As case records accumulate, it is clear that there are as in any systemic disease, a wide variety of clinical pictures Beryllium effect may produce chest x-ray changes only or mild dyspnea slight weight loss and easy fatigue with chest x-ray abnormalities A small but important group of cases has appeared in which chronic beryllium disease has followed, after a period of from months to years one or more attacks of acute beryllium poisoning There are by conservative estimate case records of over 300 of the acute disease and at least 150 of the chronic (see Machle[10]) Unquestionably many cases were missed before the correlation between beryllium exposure and illness became apparent

Acute Beryllium Poisoning

The most comprehensive description of this group of cases was published by Van Ordstrand and his colleagues[9] in 1945 Manifestations of illness occurred while the workers were engaged actively in operations involving beryllium compounds Forty-two patients had contact dermatitis or an indolent type of skin ulcer following trauma The ulcer termed beryllium ulcer required incision and curettage with removal of a center containing a beryllium crystal The contact dermatitis healed when exposure to beryllium ceased Conjunctivitis occurred often at the same time as contact dermatitis The authors observed that workers with dermatitis if continued in contact with beryllium compounds developed symptoms of respiratory tract irritation Ninety patients in this series had evidence of nasopharyngitis and tracheobronchitis which cleared following removal from beryllium exposure Chemical pneumonitis occurred in 38 workers The symptoms were insidious

onset with cough and occasional blood streaked sputum substernal pain dyspnea and cyanosis Anorexia with weight loss of from 5 to 14 pounds occurred in every case Rales reduced vital capacity and a distinctive chest x ray were the signs of pulmonary involvement Beryllium pneumonitis may prove fatal or may go on to complete symptomatic recovery and x ray clearing in from 1 to 12 months Prompt removal from beryllium exposure and complete bed rest with oxygen therapy as indicated influence the prognosis

Many case reports from research laboratories other plants extracting beryllium from the ore with variation in method manufacture of alloys and manufacture of phosphorus have substantiated European experience and the report of Van Ordstrand and associates[8, 12] (see Kress and Crispell[9] Machle[10] Weber and Engelhardt[1] Gelman[3, 4] Berkovitz and Izrael[5], Van Ordstrand[8, 12] and Aub and Grier[61]) in the delineation of acute beryllium poisoning It seems likely that the irritation and specific tissue response depend on contact with and inhalation of certain beryllium compounds in relatively large amounts

The variation in quality and quantity of beryllium exposure helps to account for clinical syndromes encountered in worker illness which may be properly called subacute Such worker patients have transitory periods of weight loss dyspnea and x ray changes presenting great difficulty in differential diagnosis

Chronic Beryllium Poisoning

The smaller group of cases of chronic beryllium poisoning probably about 150 known at present (December 1950) are linked symptomatically with the group of cases of acute beryllium poisoning by weight loss and shortness of breath The striking differences are in the mode of onset x ray picture the malignant course and poor prognosis As knowledge accumulates it is clear that there is no sex or race difference in the incidence of beryllium poisoning

The incidence of beryllium poisoning varies with several factors some of these unknown in an exposed worker population In the extraction industry the quantity of the harmful beryllium compound in the workers breathing zone is a crucial factor in producing acute beryllium poisoning In the epidemiology of the chronic disease in the manufacture of fluorescent lamps where the largest number of cases has been seen the number of cases changes from year to year in the

same exposed group because of the variation in delay in onset of signs and symptoms after the worker leaves beryllium contaminated atmosphere From a plant population of about 2 000 workers 17 cases were reported in 1946 33 in 1947, 45 in 1948, and at this time (December 1950) there are about 75 diagnosed cases There are instances of apparently very slight exposure suggesting that a few individuals are exceedingly vulnerable to certain beryllium compounds in minute doses under as yet undefined circumstances In the studied cases of chronic beryllium poisoning there has been no unusual incidence of allergy in the patients history or in the family history of ill workers The Cleveland observers noted that workers, who developed skin reactions to beryllium compounds in the extraction industry, might more readily go on to acute respiratory manifestations of beryllium intoxication suggesting a sensitivity response

The notable feature of chronic beryllium poisoning is the delay in onset from the time that the worker leaves the beryllium exposure to the onset of symptoms varying with present data (December, 1950) from six months to nine years Since new cases are being uncovered currently, the delay period may increase A remarkable finding has been that women who have worked in operations using beryllium after an uneventful pregnancy make up 25 per cent of the cases in one series in a fluorescent lamp manufacturing plant A few workers showed the onset of chronic beryllium intoxication while still at work

The onset of chronic beryllium poisoning usually is gradual Weight loss may precede the development of dyspnea cough and the striking chest x ray picture Some cases come to the attention of physicians by discovery of the x ray changes in the course of routine community surveys the worker patient being free of complaints In many cases of chronic beryllium poisoning the medical history reveals some episode, which may be a predisposing factor in the onset of disease such as frequent or severe respiratory infection, rheumatoid arthritis and as suggested pregnancy

The course of the chronic illness is severe in most cases and persists with remissions and exacerbations from 12 months to as long as six years with a mortality rate of about 25 per cent A small number of patients have recovered from beryllium poisoning clinically although x ray changes still are detectable in one instance seven years after return to activity A similarly small number of beryllium exposed workers have had x-ray findings linking them with the ill workers but after a period

of years have developed no symptoms or very slight weight loss and dyspnea on strenuous effort

Involvement of skin eye lymph nodes liver spleen and kidneys has been reported Renal calculi appear in about 10 per cent of the studied cases Cor pulmonale with congestive heart failure is a frequent complication and cause of death Spontaneous pneumothorax is a troublesome complication

Differential diagnosis is important and often difficult In each case an acid fast infection must be ruled out by bacteriological study To date tuberculous infection has appeared as a complication of chronic beryllium poisoning in only two cases who were exposed in tuberculosis sanatoria for a period of months Boeck s sarcoid is to be distinguished by the greater severity of the course of beryllium poisoning with more frequent gastrointestinal symptoms and lack of any x ray changes in the bones The most telling point in correct etiological diagnosis is a precise history of beryllium exposure

The chest roentgenograms of most cases of chronic beryllium poisoning present features in common at some time in the disease Wilson[28] has discussed the problem of x ray interpretation as have Pascucci[27] and Roberts[41] The most striking x ray finding is the widespread bilateral involvement with densities described by Wilson and Sosman as observed roughly in three stages first a sand storm' appearance secondly a diffuse reticular pattern on a granular background and finally a snowstorm' appearance due to small distinct nodules throughout the lungs Frequently there is enlargement of hilar nodes and noticeable emphysema at the apices and bases with occasionally areas of pneumothorax visible

Neighbor Cases of Chronic Beryllium Poisoning

It is now established that a small number of persons living in the near neighborhood of plants using beryllium compounds have developed chronic beryllium poisoning[8] Such cases have been reported in the community adjoining a plant manufacturing fluorescent lamps[30] and in a second living area close to a beryllium extraction plant[31, 16] There are reasonably well studied cases of women suffering from chronic beryllium poisoning whose only exposure has been through the clothes of persons who were workers in the beryllium industry Fantastic as this seems it appears to be true and recalls established cases of housewife

death due to anthrax following washing and care of clothes of the husband who was a worker in a tannery Lisenbud and associates[31] estimate from their studies of beryllium air concentration during home laundering of work clothes that 17 micrograms of beryllium could be inhaled in a day As knowledge of the amounts and character of beryllium compounds emptied from beryllium handling plants before the recognition of beryllium toxicity accumulates, these "neighborhood cases become understandable Gelman[3,4] noted that watchmen 100 meters from any operation involving the use of beryllium developed signs and symptoms of beryllium poisoning These observations may be important in establishing the diagnosis in cases presenting weight loss dyspnea and marked x-ray changes in the absence of evidence of acid fast infection

Laboratory Findings

Acute beryllium poisoning usually presents normal blood counts and sedimentation time Disturbance in liver function is demonstrated by abnormal cephalin flocculation time bromsulfalein retention and elevated globulin levels in electrophoretic studies of the serum The pulmonary vital capacity is immediately markedly reduced

Chronic beryllium poisoning has presented striking changes in the blood chemistry giving good evidence for the contention that beryllium poisoning is a systemic rather than an exclusively pulmonary disease Biochemical changes are recorded (see Hardy and Tabershaw[13] and Machle[10]) in total protein with globulin elevation calcium and alkaline phosphatase increase or decrease decrease in prothrombin time and changes in bromsulfalein retention and cephalin flocculation time Waterhouse[38] found in careful metabolic studies that patients with chronic beryllium poisoning are in negative nitrogen balance She further reports hypercalcuria in some of the patients which doubtless correlates with the appearance of kidney stones in about 10 per cent of the cases Sedimentation time and blood counts are modified as would be anticipated by secondary infection chiefly respiratory and the development of cor pulmonale producing in some cases a polycythemia The vital capacity is markedly reduced and patients have been seen with such rapid shallow respirations that they were unable to make any record on the spirometer It is notable that the number of positive tuberculin tests reported is low but there are no exact studies of this finding

By spectrographic method such as Cholak's[9] the presence of beryllium in the tissues of workers who have died of beryllium poisoning has been established. Beryllium is found in lung, liver, spleen, nodes, kidney and bone. The amounts vary considerably from 10 to 00 micrograms per 100 grams of lung and up to 13 micrograms per 100 grams of bone (see Martland[14] and Machle[10]). Spectrographic analysis of urine demonstrates the presence of beryllium in exposed individuals. This element is not found in the urines of non-exposed individuals. Klemperer and Martin[43] have developed a chemical method for the detection of traces of beryllium in biological material.

Treatment

Oxygen and bed rest are the only methods of treatment which to date have been helpful. Many specifics have been tried, including BAL, sulfonamides, cytochrome C, penicillin, streptomycin, without avail (Van Ordstrand and associates[8], Pyre and Ordway[9], Hardy[30], Machle[10]). *Prevention of respiratory tract infection is extremely important in cases* of chronic beryllium poisoning. Too early activity in acute beryllium poisoning is held responsible for a fatal outcome by Van Ordstrand and associates[8]. In 1950 ACTH and cortisone were used in treating cases of chronic beryllium poisoning. Kennedy and associates[5] reported one case so treated in which x-ray and clinical remission were correlated with improvement in objective pulmonary function studies. In this case and others now informally reported[60] transient clinical improvement *is the rule but as in other diseases ACTH and cortisone do not result in* a cure. Reports indicate variable response lasting for varying periods of time. In general the best results are observed in cases of chronic beryllium poisoning treated early. If extensive emphysema and advanced pulmonary disability are present, indicating irreversible pathology, as might be expected improvement is slight and without therapy relapse is prompt. Return of abnormal biochemical findings to normal levels, reduction in liver size, reversal of clubbing of the fingers have been observed as well as general improvement in well-being, increase in appetite and weight and disappearance of dyspnea and cyanosis. No evidence is presently available as to exact dosage schedule and choice of drug. In a disease with the poor prognosis of chronic beryllium poisoning it is undoubtedly proper to consider the use of ACTH and cortisone with due respect for the possible ill effects of intense or long

continued therapy There is no currently available knowledge of the mode of action of ACTH and cortisone in beryllium disease

Schubert[4] made many interesting observations, while collaborating in a vain attempt to complex beryllium in the body with citrate salts to modify toxicity and hasten its excretion, as has been tried with some success in lead poisoning[8]

Control

Since the recognition of certain beryllium compounds as potential toxic industrial hazards much has been done by industry Air studies were delayed until the development of a spectrographic method There are few figures on air concentrations correlated with actual illness Eisenbud and associates[31] have presented recently the calculated beryllium concentration after an accident to equipment in a beryllium extraction plant resulting in 3 cases of acute beryllium poisoning within the next 72 hours Titus has calculated the amount of beryllium in the air during machining of beryllium steel but this was not correlated with illness Eisenbud also presents data on the beryllium compound capable of producing disease in certain beryllium producing operations The fluorescent lamp industry has met this problem by developing a phosphor which does not contain beryllium Industries, that must expose workers to beryllium compounds, are trying to bring the air concentration as near nil as possible until reliable data are collected to permit the establishment of a figure for maximum allowable concentration based on knowledge of the one or more beryllium compounds of toxic possibilities

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XI

Cadmium

By FRANK PRINCI

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Cadmium is a bivalent metal[1] of a bluish white color and has the property of lowering the melting point of certain alloys when incorporated in small proportions. It occurs in small quantities in zinc ores (1 to 3 per cent) and as the mineral greenockite (cadmium sulfide). The specific gravity of the latter is 4.5 to 4.9 and its cadmium content is 77.5 per cent.[2]

The principal commercial ores of cadmium are the zinc ores such as blende (zinc sulfide), sphalerite, wurtzite, smithsonite and calamine.[3] In blende cadmium is found as isomorphous greenockite; in calamine it exists as cadmium carbonate. It may be obtained by direct distillation, solution and electrolytic precipitation or by solution and chemical precipitation. In addition to its property of lowering the melting point, it also gives valuable protection to iron and steel against atmospheric corrosion when electrically deposited thereon as a coating.[3]

Uses

Cadmium is rarely used as a metal directly. Its greatest importance is as a constituent of alloys and in the forms of its compounds.[4] According to Strong, one alloy in particular, composed of 90.8 parts of lead, 7.8 parts of cadmium and 1.4 parts of zinc, is an excellent one for general soldering purposes which involve the use of iron.

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USES

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Although cadmium sulfide is used most extensively as a paint pigment because of its great resistance to heat, light and humidity[5], it has also been used as a collyrium in medical practice because of its strong astringent action[6] Other pigments are made from the sulfide by mixing cadmium sulfide with cadmium selenide and barium sulfate These colors range from orange to purplish red Pale colors are made from cadmium oxalate and dark colors from cadmium carbonate Cadmium oleate exhibits greater resistance to hydrolysis than zinc oleate and may attain greater industrial use as an impregnating material than the zinc compound It has been shown to be an excellent material for water proofing textiles and for impregnating porous ceramic articles If its use in these connections should become widespread the question of absorption through the skin and the gastrointestinal tract may become of even greater importance than it appears to be at present

Other compounds of cadmium have varied and extensive industrial uses In common use today are the chloride in photography dyeing and plating the nitrate for coloring glass and porcelains and the tungstate in making fluorescent paints The tungstate is used also in making phonograph records[7] Various other compounds have been used in making storage batteries metal bearings and car and war industries

Historical

The earliest written reference to the effects of cadmium on humans is found in the 13th Century manuscripts of the Scholae Salerni[9] Included among the list of drugs which were said to produce moderate vomiting was cadmia impure zinc oxide In 1713 Ramazzini referred to the damaging action on the lungs of the dusts of "cadmia" and other metallic substances Although Sovet[10] is credited frequently with being the first to describe cadmium poisoning Van Hasselt[11] records an experiment by Burdach in 1822 in which the latter ingested thirty to thirty-two milligrams of cadmium sulfate and developed nausea and vomiting

In 1867 Marme[1] distinguished between the toxic symptoms which were due to cadmium and zinc poisoning He declared that cadmium produced gastroenteritis malnutrition fatty liver and fatty heart These manifestations of cadmium toxicity have been demonstrated by almost all later experimenters Wheeler's[13] two cases of accidental poisoning are commonly mentioned in the literature as classic cases and are probably the first cases reported in the United States The substance which

was employed in these poisonings, was identified positively as cadmium bromide

In recent years the production of cadmium has increased tremendously because of its uses in both civilian and war production[14] World production of the substance was eighty tons in 1914[3] and over four thousand tons in 1946[16]

Clinical Features

Sovet's[19] early clinical description of poisoning by cadmium carbonate remains a classic in the literature of cadmium He described the cases of three servants who were using a paste to polish silverware The paste was applied to the utensils and was brushed off when dry The first symptoms to develop were dryness of the throat and constriction of the chest Later respiratory difficulty and vomiting occurred One of the servants who had had the greatest exposure showed paleness cold extremities extreme prostration cramps in the lower limbs headache continuous nausea frequent vomiting of liquid material (which was white and/or green at different times) diarrhea (yellow and very fetid) pale and wet tongue, urinary tenesmus and scanty urine The pulse was feeble and almost imperceptible All three ultimately recovered These observations on poisoning by massive exposure have been verified by later clinical and experimental reports

As the industrial use of cadmium became more common other manifestations of cadmium toxicity were noted among exposed individuals Noteworthy were weakness anorexia shivering brown urine and generalized pneumonia[3] Prodan's[15] work already had demonstrated experimentally the development of the symptoms of bronchopneumonia He also declared that after inhalation cadmium was found mainly in the lungs liver and kidneys shortly after the exposure and that later it became stored chiefly in the liver kidneys and bones The typical clinical symptoms of bronchopneumonia were found also in Johnstone's[1] case An interesting finding in this patient was that sleep was impossible The individual had been exposed to heavy fumes for about forty minutes but no report was made of the atmospheric concentration

In a review of the literature Spolyar[9] reported 59 recorded cases of cadmium intoxication by inhalation These were in addition to his own 5 cases In every instance there had been severe exposures to cadmium

fumes In his cases he found few immediate symptoms, but there was a delayed syndrome which appeared 20 to 36 hours after the exposure Except for 1 patient, who died, none of the remaining 4 showed residual chest pathology after recovery

In 1942 a new symptom complex was described by Lafitte and Gros[1] This was one of the few reported observations of chronic intoxications, and a new clinical picture was presented In workers exposed to cadmium fumes and dusts over long periods of time there was found a syndrome manifested clinically by vague motor difficulties, great pain (lancinating) in the lower limbs but without precise localization and similar pains in the pelvis and the loins Walking was considerably impeded Physical examination was negative

Similar observations were made by Barthelemy and Moline[2], who described this syndrome more thoroughly and added to the knowledge of this subject the still earlier clinical sign of yellow pigmentation of the teeth They divided the progress of chronic cadmium intoxication into the following phases

1) *Latent Period* — Lasts about two years The workers complain of no objective symptoms If the toxic work was abandoned no symptoms appeared up to 3 or even 5 years after the workers had left the shops where they had worked with cadmium for 1 or 2 years

2) *Period of Alarm* — Occurs about the second year of exposure A *yellow cadmium ring* appears *on the teeth* (Figs 1 and 2) It is a true pigmentation of the enamel which begins at the base of the tooth where it is the most intense and gradually covers a third and then one half of the tooth There are no gingival changes The color varies from clear yellow to golden and persists until the exposure has been discontinued The author states that it takes as long for the yellow ring to disappear as it did for it to develop

3) *Painful Period* — Appears about the fourth year The patient first develops weakness and later lancinating pain which is not specific in location and which does not have a neuritic distribution

4) *Radiological Period* — Period of infirmity which begins about the eighth year During this period a typical *Milkman's syndrome* is seen and the individuals are described as walking with little duck like steps Walking becomes increasingly more difficult and finally the patients become entirely crippled This is the same syndrome recognized by Lafitte and Gros

Although the main route of cadmium absorption during industrial exposures is by way of the respiratory apparatus most of the reported

cases of cadmium poisoning are those which occurred by accidental ingestion In consequence of this fact by far the greatest part of the work in the investigation of cadmium poisoning has been done by means of feeding experiments Aside from those cases of purely historical interest the earliest reports of poisoning by ingestion are those of Wheeler[33] His patients accidentally took cadmium bromide in amounts estimated to be from 4 to 16 grains Both patients developed severe vomiting and diarrhea which lasted about five hours During part of the time the pulse was imperceptible in either individual Both patients ultimately recovered

Leschke[3] described the occurrence of giddiness and loss of consciousness with 30 milligrams as the dose which would cause vomiting Pancheri[15] described symptoms which occurred in the following order, pain and sense of tension in the epigastrium, nausea constipation occasional diarrhea lack of appetite and dryness of the throat Similar symptoms were seen in the 50 cases reported by Frant[24] and in the 2 outbreaks reported by Schiftner[8] The latter reported that symptoms appeared within one half to one hour after ingestion of the cadmium contaminated material In a recapitulation of all reported cases the National Institute of Health[4] reported 87 cases with but one death However in addition to the fortuitous presence of cadmium in food and drink it must be remembered that some of the airborne material is frequently swallowed This fact has prompted Ross[8] to write though the lungs have been indicted as the main burden of this onslaught I would point out that the digestive tract shares with the pulmonary system the first line of defense

Animal experimentation has confirmed the physiological findings in humans but has added little that is useful to the study of human intoxication Loss of appetite loss in weight and vomiting have been consistently reported[6] Prodan s[18] work is again the most complete in the study of the effects of ingested cadmium He reported that cadmium when fed in large doses produced salivation vomiting and anorexia Cadmium was retained in the liver in greater absolute quantity the bones also retained a high percentage He stated that vomiting and loss of appetite were followed by loss of body weight although Alsberg[6] had found that the anorexia was less marked than the failure to gain weight

Much of the information concerning the effects of cadmium and its compounds has been obtained by means of subcutaneous and intravenous administration in animals Early work[27] with dogs and frogs showed

fumes In his cases he found few immediate symptoms, but there was a delayed syndrome which appeared 20 to 36 hours after the exposure Except for 1 patient, who died, none of the remaining 4 showed residual chest pathology after recovery

In 1942 a new symptom complex was described by Lafitte and Gros [1] This was one of the few reported observations of chronic intoxications, and a new clinical picture was presented In workers exposed to cadmium fumes and dusts over long periods of time there was found a syndrome manifested clinically by vague motor difficulties great pain (lancinating) in the lower limbs but without precise localization and similar pains in the pelvis and the loins Walking was considerably impeded Physical examination was negative

Similar observations were made by Barthelemy and Moline[2], who described this syndrome more thoroughly and added to the knowledge of this subject the still earlier clinical sign of yellow pigmentation of the teeth They divided the progress of chronic cadmium intoxication into the following phases

1) *Latent Period* — Lasts about two years The workers complain of no objective symptoms If the toxic work was abandoned, no symptoms appeared up to 3 or even 5 years after the workers had left the shops where they had worked with cadmium for 1 or 2 years

2) *Period of Alarm* — Occurs about the second year of exposure A *yellow cadmium ring* appears *on the teeth* (Figs 1 and 2) It is a true pigmentation of the enamel which begins at the base of the tooth where it is the most intense and gradually covers a third and then one half of the tooth There are no gingival changes The color varies from clear yellow to golden and persists until the exposure has been discontinued The author states that it takes as long for the yellow ring to disappear as it did for it to develop

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Although the main route of cadmium absorption during industrial exposures is by way of the respiratory apparatus most of the reported

rical and ordinarily multiple, affecting the femurs the tibiae the pelvis and the scapulae Although at first these striae gave the appearance of spontaneous fractures, there was never any callous or any displacement or fragments The roentgenological picture was said to be typical of that found in Millman's* syndrome

These observations were borne out in 1946 in a study of a group of workers who had been exposed to cadmium hydroxide fumes for over 10 years in a plant making ferro-nickel storage batteries Among these individuals there was also found a yellow ring of cadmium on the teeth (Figs 1 and 2) This was described as a true pigmentation of the enamel beginning at the neck of the tooth where it had its maximum intensity and covering gradually one third and then one half of the tooth beyond the gum margin The gum itself was said to be unchanged and no cadmium gingivitis could be found

Pathology

In contrast to the paucity of autopsy data on human subjects a considerable bulk of animal experimentation has been reported Some of the earliest work was done by Athanasiu[8] who found that in vitro cadmium salts favored the separation of red blood cells from solutions There was also a separation of hemoglobin which was turned partially into hematin and partially into globulin He also determined that in severe poisoning the heart stopped in diastole In the same year Severi[13] performed autopsies on animals dogs and rabbits which were killed by subcutaneous injections of cadmium chloride Post mortem examination showed injection of the intestinal walls and the presence of liquid or near liquid fecal material and mucus which adhered to the walls No intestinal ulcerations were found even in the large colon or sigmoid The kidneys were grossly normal but showed microscopical changes similar to those found in mercury poisoning Hemoglobin crystals in the renal tubules and calcium deposits in the kidneys of the rabbits were noted

A thorough description of the pathological effects of cadmium has been given by Prodan[18] who administered the metal to cats by several different routes in the form of soluble and insoluble compounds He found no definite blood changes Irrespective of the dose of cadmium

* Millman 1930 described a generalized bone disease characterized by multiple transparent stripes of absorption in the long and flat bones

that with intravenous and subcutaneous injection pain sensation and reflexes were lost The reflexes disappeared before the loss of pain sensation occurred Later, motor paralysis and general depression, rapid breathing, rapid pulse and lowered temperature developed Finally, the animals showed a loss of oculo palpebral reflex, mydriasis shallow respiration, much lower temperature, progressive cardiac weakening and death without convulsions The myocardium and the striated muscle were excitable after death showing that the poison acted on the vasomotor nerves directly Athanasiu[1] confirmed the findings of increased pulse rate, and Paderi[9] verified the central nervous system action of cadmium with experiments on frogs and birds The latter maintained that cadmium was not a direct cell poison

The metabolism of intravenously injected cadmium (cadmium salicylate) was studied by Hessel[6] who found that the injected substance disappeared very rapidly from the blood stream Elimination was found to be continuous through the alimentary tract and kidneys and although cadmium appeared in the urine within 1 to 2 days after injection it could not be detected in the feces before 4 to 5 days

Absorption through the unbroken skin has been studied also and has been said not to be an important factor in ordinary exposures An undershirt, which contained 50 milligrams of cadmium chloride distributed over its entire surface, was worn interruptedly for a period of 40 hours No effects were noted and no cadmium was found in the total urine for 60 hours[31] The use of a cadmium solution also has been reported as being entirely non-irritating to severe cases of athlete's foot, although the feet were immersed daily for 10 minutes and then massaged vigorously[32]

Johnstone's[19] case, one of acute intoxication resulting from massive exposure gives the most complete pathological report on a human case In the lungs most of the alveoli were collapsed, and there was desquamation of the lining epithelium Even in those alveoli which were open the lining epithelium was swollen and stained poorly, these alveoli contained plasma cells a few leucocytes large pale staining debris Considerable edema was present in both lungs The examination of the heart was essentially negative On the day of death there was a slight drop in hemoglobin and erythrocyte count while the leucocytes and percentage of polymorphonuclear cells increased tremendously

The results of chronic exposures were studied by Lafitte and Gros in 194-[1] At this time they described the radiographic presence of osseous striae and transverse fissuring which frequently were symmet-

In a recent study[25] of men who were exposed to relatively high concentrations of cadmium dusts over long periods of time, it was found that very few of the previously described symptoms were present. The presence of a yellow ring on the teeth of those men who had had long exposures was verified. This ring was probably part of the tooth structure itself and was not related to the hygienic condition of the

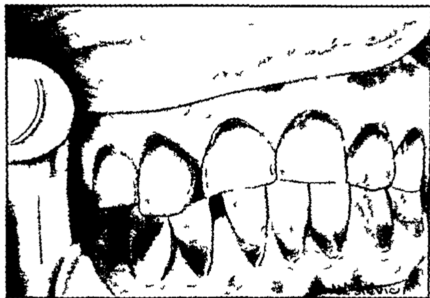


Fig. 1 Teeth in cadmium intoxication

teeth or gums. It may well be considered the earliest sign of cadmium absorption although much greater exposure to cadmium can occur without apparent damage to the individual. Fig. 1 shows the beginning of the yellow ring in a worker who had been exposed for about two years. A more marked discoloration is shown in Fig. 2. This latter individual had an exposure of 10 years. Both of these women were non smokers. None of the other reported symptoms of cadmium intoxication could be definitely identified but all the men showed evidence of cadmium absorption. Blood levels as high as 0.4 mgm per 100 gm of blood were found and urine levels of 100 mgm per liter of urine. It is suggested that there is a rapid elimination of cadmium from the body and that there is no cumulative effect.

The atmospheric concentrations to which these men were exposed

fed, the liver and kidneys were affected, but all the doses were large enough to produce acute manifestations of poisoning The liver changes varied from a general granulation of the cells to a pronounced fatty infiltration, especially around the central vein The kidneys showed fatty infiltration which was more prominent in the convoluted tubules By inhalation cadmium sulfide produced a bronchopneumonia accompanied by edema and extensive emphysema and sometimes pleural effusion The lungs usually were the only organs affected Microscopical sections of the lungs showed edema and injury to the bronchioles and alveolar ducts manifested by desquamation of the epithelium, polymorphonuclear infiltration in the walls and edema of the walls Acute alveolar emphysema was present, and a small amount of fibrin was found in the alveolar spaces These descriptions compare closely with Johnstone's[19] case of acute poisoning by massive exposure

Both Otto[34] and Prodan[13] showed that hemoglobin and red cell counts were increased in experiments which employed cadmium sulfide by inhalation These findings were not confirmed in the poisonings by inhalation which has been described in humans[19, 35] Nor did Briganti[14] verify these findings in his animal experiments He found no increase in red blood cells although all his animals developed pneumonitis and frequently a true pneumonia His work done entirely with hypodermically injected cadmium sulfide and cadmium oxide showed a diminution of all blood elements including hemoglobin The findings were the same for both compounds Death occurred before an anemia incompatible with life could develop There was a relative lymphocytosis a diminution of granulocytes and an increase in monocytes, Turcl cells were found frequently The bone marrow of the femurs of all animals showed a true myelotoxicosis He concluded that cadmium has a definite harmful action on the regenerative activity of the bone marrow Zlataroff[36] also studied the various soluble salts of cadmium and found that they exerted a strong action on the catalysis of the blood

Friberg[3] states that there is evidence of proteinuria in workmen who have had chronic exposure to cadmium and nickel dust Polarographic studies of the blood of these persons showed pathological changes which implied the possibility of the occurrence of low molecular weight protein which is not found to be present among healthy persons Similar pathological changes have not been reported hitherto in the literature, but recent work indicates that in chronic absorption very little cadmium is deposited in the liver, but that large amounts are found in the kidneys

Treatment

The treatment of acute poisoning by ingestion is entirely symptomatic and supportive Death is rare because cadmium compounds act as violent emetics and not enough of the poison is absorbed The acid base balance and fluid loss should be restored and care should be taken not to aggravate the gastroenteritis BAL (2 3 dimercaptopropanol) has been advocated for the treatment of acute intoxications[10] Although the clinical use of this substance has not been reported daily doses of 100 to 150 mgm are recommended Treatment should be instituted as soon after exposure as possible

In acute poisoning by inhalation there is injury to the respiratory epithelium and death is always preceded by bronchopneumonia Thus oxygen therapy should be instituted immediately even though the patient appears to have been only moderately overcome by fumes Increasing the oxygen tension in the inspired air will decrease the opportunity for the development of edema and will improve the chances of recovery Appropriate chemotherapy may be employed if secondary invaders are suspected

Prophylaxis

All industrial processes in which fumes are elaborated should be well exhausted so that workers will not encounter a sufficient exposure which might cause deleterious effects Ventilation should be employed at the source of the process and should not consist merely of general room ventilation Exposures can be controlled only by frequent atmospheric determinations at the breathing level of the men employed The continuous use of respirators is not recommended These may be satisfactory in short unavoidable exposures to extremely high concentrations but are not practical in long continued exposures first because workers will not wear respirators constantly and secondly these pieces of equipment furnish resistance to breathing and can become extremely uncomfortable

Medical control is not satisfactory because even the fairly advanced clinical sign of the yellow dental ring is unaccompanied by symptoms It is probable that chronic poisoning is extremely uncommon in the United States Strong efforts should be directed to the avoidance of sudden massive concentrations which result in acute intoxication

ranged from 04 mgm per cu meter of air to 31 30 mgm per cu meter of air with an average concentration of 7 18 mgm per cubic meter of air

Still more recently[39] several individuals have been studied who show evidence of long continued cadmium absorption without history of symptoms In the drinking water of these persons there has been found a cadmium content which averaged 047 mgm per liter Both blood and

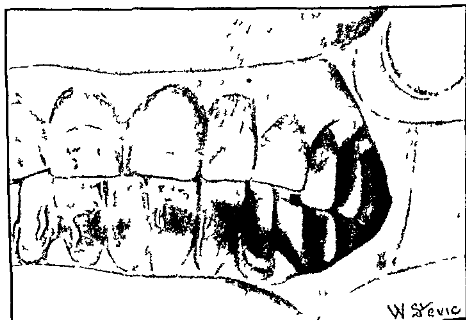


Fig 2 Teeth in cadmium intoxication

urine levels in this group have been found to exceed 0 10 mgm This is certainly contributory evidence that the slow absorption of cadmium can be innocuous

Much confusion concerning maximum allowable concentrations exists because of the different types of dusts and fumes which have been in use It seems at this time that the toxicity of the various compounds varies not only with the compound itself but also with the physical state of that compound In 194 the American Standards Association arbitrarily adopted 1 mgm per 10 cu meters as the maximum allowable concentration of cadmium in the air This figure was definitely a war time standard and an attempt is now being made to establish a higher and more reasonable limit

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XII

CHROMIUM

By RONALD F. BUCHAN

Chromium compounds are used industrially in the manufacture of wallpaper, coal tar dyes, electric batteries, explosives, textile printing, paints and pigment mixing, in lithography and commonly in photography and electroplating.

Chromium itself is generally inert but chromic acid and its compounds exert serious caustic action affecting the skin and mucous membranes. Chromium trioxide, neutral sodium chromate, neutral potassium chromate, sodium bichromate, potassium bichromate are the compounds most usually employed industrially. Sodium bichromate finds the greatest number of common uses. Chrome ulcers constitute the commonest dermatological finding. These ulcers have a punched out appearance, a grey necrotic base and a thick white healing rim. They develop slowly, increasing in size from pinhead size to large necrotic sloughs. Over flexion points they are painful. In areas free from movement or trauma usually they are symptomless. Less commonly a dermatitis punctate and papular in nature may be observed. This may arise as a primary irritant reaction or a sensitization reaction dependent upon the offending product. In the latter category, as with all industrial sensitizers, early and late sensitizations may be noted. "Hardening," a natural desensitization process may occur. In "hardened" workers absent from contact with chrome for some time due to illness, vacation or job change, a breakdown of the "hardening" often results with the subsequent development of sensitivity reactions again. Pirila and Kilpio[1] review a series of dermatological cases in numerous occupations. They emphasize the long duration of symtoms even when the patient is removed from exposure. This has not been the experience in the United States.

A second common lesion is an ulceration and perforation of the nasal septum, and if one examines workers exposed to chromic acid and its compounds a high incidence of nasal mucosa irritation and perforation will be found, often times unknown to the patient but as often drawn to his attention because of recurrent nosebleeds. He may be entirely unaware of nasal septal perforation until a whistling in his

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6 One plant handling only bichromates chromic acid and a tanning compound had an experience of 1 853 male years of exposure with 33 deaths, none of which was due to cancer of the respiratory system This experience suggests that the monochromates may be the compounds responsible for lung cancer

7 The occurrence of nasal irritation and perforation does not necessarily imply exposure to kinds and quantities of chromium compounds capable of producing lung cancer Rates for nasal irritation of 14 4 per cent and for septal perforation of 15 per cent may occur among exposed workers with no lung cancer reported

It is of special interest to note that the report would tend to incriminate the monochromates in view of the many common bichromate exposures

Mills[4] however takes vehement exception to these conclusions He points out that white men living in the Chicago Loop with no chromate exposure have for the years 1944 46 a mortality due to lung cancer higher than encountered in two of the plants studied by Machle and Gregorius[3] Emphasizing the importance of the as yet undefined role of air pollution in industrial areas as a factor to be considered he is reluctant to ascribe to chromate exposure a specific place in the etiology of lung cancer

Baetjer[5, 6] in a valuable and extensive survey of the literature and a 15 to 20 year study of the hospital records of the Johns Hopkins Hospital and Baltimore City Hospital confirms the general opinion expressed in the conclusions of the Machle Gregorius study and the German literature, namely that the number of deaths due to cancer of the lungs and bronchi is greater in the chromate producing industry than would normally be expected

The chromate industry of the United States largely located in Maryland New Jersey New York and Ohio has initiated an intensive study of the problem conducted by the United States Public Health Service Environmental epidemiology and physical appraisals should assist in the definition of this serious question

Prevention of dermatological hazards is dependent upon the removal of fumes mists and dust by engineering control methods personal hygiene and the use of protective clothing gloves and boots Workers should recognize the hazards incident to their occupation in order that they may guard against them The nasal mucosa may be protected by vaseline or by vaseline impregnated cotton plugs Workers generally

speech leads him to seek advice Large spills of chromic acid and its compounds directly on the skin may create large, necrotic, deep seated ulcers Often times work clothing will become impregnated with chromic acid compounds and exert a gradual effect upon the skin area beneath with a slow development of ulcerated areas on contact and sensitivity manifestations Constitutional symptoms have been little noted with the exception of accidental ingestion of chromic compounds Broch finds asthma a not unusual complaint in a foundry where ferro-chromium undergoes electrothermic processes He gives a detailed account of two asthmatic patients attributing and tracing their condition to inhalation of chromium trioxide Recently, however, investigations would indicate that there is a higher than average incidence of respiratory tract carcinoma in workers exposed to chromic compounds Machle and Gregorius[3] in a careful epidemiological study in plants engaged in the extraction of chromates from ore reached the following conclusions

1 Twenty one and eight-tenths per cent of all deaths in the chromate industry were reported as being due to cancer of the respiratory system This ratio is 16 times the expected ratio of 1 3 per cent The individual ratios in five of the six plants ranged from 13 to 31 times the normal

2 The crude death rate for cancer of the lung was 25 times the normal the range of excess for the various plants being from 18- to 50-fold

3 In 5 of 6 plants the death rates for lung cancer in the group 50 years of age and under ranged from 20 to 70 times that for a comparable industrial group

4 The mortality rates for lung cancer at ages over 50 years ranged from 10 to 40 times that for a comparable industrial group

5 The high rate for cancer of the respiratory system results in a high rate in the industry for "cancer—all forms" Due to the small number of deaths there are no convincingly significant or consistent abnormalities in the rates for cancer in sites other than the lung From the data at hand it would appear that the problem in the chromate industry is limited to the cancers of the respiratory system Although 66 of the 193 deaths in our group and period of study were due to cancer (a ratio of 34 2 per cent) 42 of the deaths were from cancers of the lung If these are excluded from consideration then the ratio of deaths from all other cancers becomes 12 4 per cent for the chromate industry a ratio slightly less than that for a comparable industrial group (15 per cent)

XIII

COPPER

By RONALD F BUCHAN

Copper is a commonly used industrial element Brass and bronze both contain copper bronze being copper alloyed with tin and some times with zinc and brass a combination of copper and zinc

The usual industrial uses of pure copper give rise to no toxic reaction although tatooing of the skin is seen after penetration of the skin by small copper particles It is probable that other materials used in con junction with or in alloys with copper are contaminants such as arsenic or lead and may be the source of systemic reactions Selenium as a contaminant of copper ore may be productive of gastrointestinal com plaints and sore throats in workers employed in extraction Pure copper ordinarily does not occasion dermatological reactions although such have often been attributed to it In such instances contaminants or alloyed materials usually are the source of the skin irritation Barsky[1] reports widespread congestion of the nasal mucosa with superficial sloughs on the anterior portion of the septal walls and middle and inferior turbinates of the nose In a series of cases exposed to sodium copper cyanide free sodium cyanide and sodium hydroxide he noted many local nasal mucosal ulcerations with two instances of perforated septa One case with remarkable turgescence of the upper respiratory tract developed pneumonia and died It should be noted that multiple exposures usually exist in any plating operation and meticulous epi demiology is necessary to define the offending agent Dermatitis and ulceration of the mucous membranes are encountered commonly in electroplating operations and such lesions may be due to one or more of the multitude of primary irritants encountered rather than as a specific reaction to a specific element or its compounds Bruzzone gives a comprehensive survey of corrosive nasal lesions of industrial origin Quoting Hajeck he states that perforation of the septum is a dystrophic lesion distinguishable from the result of localized infections and occur ring in six stages preulcerative induration ulceration of the mucosa denudation of cartilage perforation of cartilage complete perforation of the septum and cicatrization of the edges Constitutional reactions[2] to copper fumes have been described as copper fever probably one

object to plugging their noses with cotton If such be the case, a moderate amount of vaseline may be placed in each nostril

In order to heal chrome ulcers it may be necessary to curet the base of the ulcer inasmuch as there is usually residual chromic acid compounds contained therein which exert a continuing caustic action If the ulcer is not too deep, scrubbing with 5 per cent sodium hyposulfite, water or saline solution may remove any residual chrome compound and suffice to clean the wound Dressings of from 5 to 10 per cent solution of sodium citrate, potassium and sodium tartrate or sodium lactate may be utilized to reduce the chromic content in the base of ulcers Curettage may or may not be necessary following such procedure Added treatment requires antibacterial applications and dressing during re epithelialization Because of the nature of the wound there is a resultant scar Secondary infection is not usually a problem but one should take ordinary preventive measures Obviously there is little to be done for nasal perforations, but evidence of mucosal irritation should call for immediate and constant supervision to prevent further damage

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XIV

LEAD POISONING

By MAY R. MAYERS

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manifestation of "metal fume fever" (see Zinc and Zinc Fever) Experimentally feeding copper salts will produce a pigment cirrhosis similar to hemochromatosis but industrially few, if any, valid instances have been reported Mallory[4] described among others four workers with long occupational exposure to copper in varied forms who exhibited deposits of hemosiderin and hemofuscin without liver cirrhosis Continued industrial experience has lent no substantial confirmation to his views or findings relative to chronic copper poisoning in man

Prevention of copper intoxication due to industrial exposure, therefore, would be dependent upon avoidance of accidental ingestion of copper salts such as the sulfate or the subacetate, which are poisonous, and if such occurred, treatment should be directed toward amelioration of shock and dehydration following upon the acute gastrointestinal irritation with vomiting and diarrhea

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one of the earliest occupational diseases to be recognized and studied and the literature contains intensely interesting clinical case histories and pathological reports reflecting the cumulative experience of a long series of distinguished physicians who, without benefit of laboratory aids to diagnosis became famous in the annals of medicine for their clinical acumen

Over the years great progress has been made toward a better understanding of lead poisoning as a medical entity The clinical laboratory has come to the assistance of the physician in problems of diagnosis Biochemical research has contributed a sound rationale for therapy For purposes of prevention quantitative analytical methods have made possible accurate chemical evaluation of the lead content of the air of the work room By their combined efforts physicians chemists and engineers have developed safety standards for exposure to lead and means for controlling lead operations so that these standards can be maintained It is gratifying to record these scientific developments and the fact that as a matter of practical experience they have demonstrated their value in the prevention of lead poisoning What remains is to extend their application in the lead industries to achieve far more complete coverage The road ahead still is a very long one but the sign posts are there

Exposure to Lead

Since so-called normal lead absorption is an important factor in differential diagnosis it might be well at the outset to review briefly some of the common sources of exposure to lead outside of industry and the opportunities for the average individual to come in contact with it and to absorb it in the course of his daily life

Lead is found normally in soil in vegetation and the tissues of healthy animals It is found in rocks and volcanic dusts in sea water and marine life in drinking water whether piped or from mineral springs and in various types of food utensils and food containers The common foods inevitably therefore contain small amounts of lead Breadstuffs meats processed meats ice cream candy leafy green vegetables and certain fruits have been singled out as containing more than the average amounts of lead[1] Regardless of any special known contact with lead consequently the average individual has many opportunities for absorbing and excreting it in small amounts Quantitative data thus is essential to any proper interpretation of the significance of its presence in any suspected case of lead poisoning

Introduction

Lead is an interesting metal Its wide distribution in nature and its unique chemical and physical properties have always made it readily available and well suited to the needs of early craftsmen Geologically it has provided a calendar as it were in that the age of ancient rocks may be determined by measuring their content of rare isotopes of lead formed by radioactive decay It has been the metal of choice in protection against excessive exposure to x-rays and gamma rays Industrially lead with its compounds and alloys has had a long and distinguished history and it continues to play a role of fundamental importance in modern technological research and development Lead poisoning was

the way in which the lead is used the particular lead substances in volved the quantities used and the extent to which control measures are effective

Despite the fact that basic principles underlying industrial control of lead operations are well understood their application is very uneven Exposure to toxic concentrations varies greatly from industry to industry, from plant to plant within a given industry and from process to process within a single plant Even in important industrial centers some lead plants still are housed in primitive quarters which make any kind of effective control virtually impossible Lead still is being dumped shoveled and swept up with dry brooms creating clouds of dust Lack of ordinary good housekeeping is one of the most common causes of injurious exposure to lead which can be avoided readily Even in plants where very ingenious engineering controls have been instituted for the more complicated lead processes the simpler ones are apt to be neglected and continue to be carried out as of old Unfortunately paradoxes of these sort are not unusual

Since dosage is of the essence these wide variations which exist in the conditions of exposure from plant to plant make it very difficult indeed for the practicing physician to evaluate the lead exposure of a patient In addition specific plant operations are such that exposure may be intermittent rather than continuous There may be high surges for short periods of time as in non ferrous foundries for example where high exposures to lead occur only during the brief periods of pouring Nevertheless such exposures can be very high while they last Then there are the special exposures of special workers such as maintenance men and repair men who must climb into lead containing machinery in order to do a single job there for a short time Knowledge as to whether the patient falls into any such special category and if he does whether he wears a properly designed respirator is quite as important to the physician as information as to the overall adequacy of engineering controls in the plant

Of general assistance to the physician is an understanding of the chemical and physical forms in which lead may be encountered in industry because these provide a clue to the toxicological effects which may be anticipated under various circumstances Tetra ethyl lead for example which is highly volatile soluble in lipids and readily absorbed through the skin will act very differently from inorganic lead compounds which are encountered usually as respirable dusts Similarly the toxicity of a particular lead substance may be materially altered by

Non-industrial Lead Poisoning

Lead poisoning may occur outside of industry, and it is important not to overlook this possibility. Young children, for example, suffering from "pica" contract lead poisoning from time to time through eating lead paint from the porches of their homes or from their cribs. Whole families have been poisoned as a result of burning, for fuel, lead grids from discarded storage batteries; a professor once developed a very puzzling case of lead poisoning which was ultimately traced to drinking the water in his old house which had an antiquated plumbing system; a prominent socialite was poisoned practicing her hobby of rubbing down and restoring antique furniture.

Cases of this type are important primarily because they are unusual. A correct diagnosis may be long delayed because of failure to consider the possibility of exposure to lead. On the other hand, a snap diagnosis of lead poisoning is not uncommon in these cases because of misinformation as to possible sources of lead exposure on the part of the family doctor. Thus "lead" pencils are mistakenly believed to contain lead, and there is an erroneous assumption that children's painted toys are always painted with lead-containing paints. Actually it is sometimes the repainting of cribs and nursery furniture by parents, who unwittingly use lead paints, which provides a lead exposure for the child who chews on it where none had existed before. On general principles it is well to consider the possibility of lead poisoning for purposes of differential diagnosis in every obscure medical situation without regard to the age, social or occupational status of the patient. It is equally important, however, to ascertain accurately whether or not there was, in fact, any unusual lead exposure in each such case.

Industrial Lead Poisoning

It is in industry that lead poisoning assumes its major role. The extent to which lead is used is immediately manifest when one considers the many places where for example soldering is being done. Ordinarily soldering does not present a health hazard because exposure to lead is too slight. But when it is carried out on a large scale by many persons doing this work simultaneously in a single room the hazard to health may be considerable. The mere use of lead in industry does not, therefore, constitute a health hazard per se. This is determined rather by

responsible for the lead hazard characteristically associated with lead pots

In lead smelting operations and in the preparation and handling of lead alloys temperatures characteristically approach the boiling point of lead (1 6-9 C) or go even higher[5] Volatilization of lead presents a serious health hazard also in lead burning operations particularly in storage battery manufacture[6] or in the burning through of lead painted metal structures, such as bridges for purposes of demolition

The following is a brief list of the more important industries or occupations which present a potential lead hazard at the present time

1) Lead and zinc mining

2) Lead and copper smelting and refining including gold and silver refining and extracting

3) Chemical industries making lead compounds and alloys

4) Non ferrous foundries (brass foundries)

5) Lead products manufacture such as tin and lead foil lead wool and rope lead putty lead pipe solder manufacture lead shot lead weights for piano keys clocks draperies etc

6) Printing including printing on textiles wallpaper etc

7) Pottery making

8) Storage battery manufacture (dry)

9) Ink manufacture

10) Color and dye making especially green and yellow

11) Paint manufacture and the application of lead paint

12) Lead burning operations, burning through lead coated structural steel lead burning for the removal of lead paint from woodwork lead burning in battery making lead burning in boiler making etc

13) Glass manufacture and fabrication including leaded glass, cut glass and art glass work

14) Decalcomania making and printing

15) Diamond cutting

16) Tempering of steel wire etc

17) Silk weighting

18) File cutting

19) Insecticide manufacture and its application by farmers gardeners hothouse workers pilots doing crop dusting etc

20) Tile glazed sanitary ware and porcelain manufacture

21) Leather tanning coloring and shoe dyeing

22) Rubber manufacture fabrication and reclaiming of old rubber

23) Brick making

its combination with other toxic substances The relatively high toxicity of lead arsenate, for example, is believed to be due to the addition of the arsenic radicle rather than to the lead itself Organic lead compounds are more toxic than the inorganic Of the inorganic compounds the lead suboxides carbonates litharge and the basic lead sulphates are among the most toxic of those in common use The acetate, nitrate and chloride also are highly toxic, but they are used less often The chromate and sulphide appear to be among the less toxic of the common lead compounds[3]

Solubility is another important index of toxicity Lead carbonate and lead sulphate both far more toxic than lead sulphide (galena), are more soluble in gastric juice[4] Lead glaze, in former times composed of basic carbonate was highly toxic Converted into the insoluble disilicate known as 'fritted' lead, however this important lead hazard was largely removed from the pottery industry In considering relative solubility, one must, however, distinguish between solubility in water and solubility in gastric juice or other body fluids and tissues Since lead poisoning is due far more to lead inhalation than to its ingestion solubility in alveolar fluids and blood serum is of particular importance

The physical properties of lead substances may be greatly altered by the operations through which they are processed Alterations in particle size, particularly are of great significance in that particle size will determine to a considerable extent, how long the dust will remain suspended in the air at the breathing zone of the worker It will influence its solubility in body fluids following inhalation Whether or not the dust particles are dry, wet or sticky will further affect exposure and absorption Operational factors thus play varying roles in modifying the original chemical and physical properties of the lead substances being processed thereby altering their potential toxicity at different stages along the production line

The danger of exposure to lead in the form of fumes is well recognized but this is encountered far less often than is commonly supposed Lead pots for example are seldom heated above 450 C, the temperature at which volatilization of lead occurs It is not the molten lead in a lead pot therefore which creates the principal lead hazard in these operations, but rather the lead suboxide which forms an almost invisible film on the surface of the molten metal Lead suboxide because of its small particle size and lightness readily floats up into the air whenever the lead in the pot is agitated particularly when the dross" is being skimmed from the surface It is the lead suboxide, therefore, which is

responsible for the lead hazard characteristically associated with lead pots

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20) Tile glazed sanitary ware and porcelain manufacture

21) Leather tanning coloring and shoe dyeing

22) Rubber manufacture fabrication and reclaiming of old rubber

23) Brick making

24) Tetra ethyl lead manufacture and distribution
25) Mirror silvering
26) Linoleum manufacture
27) Canning
28) Paper manufacture
29) Plumbing
30) Shooting galleries (workers testing equipment)

Among the lead substances most commonly used are the following, lead (Pb), lead suboxide (Pb_2O), lead monoxide (Pb O), red lead (Pb_3O_4), lead peroxide or dioxide (PbO_2), lead sesquioxide (Pb_2O_3), white lead or basic carbonate ($PbCO_3$), lead sulphate ($PbSO_4$), lead chromate ($PbCrO_4$), lead sulphide (Pb S), lead acetate ($Pb(CH_3COO)_2$), lead arsenate ($Pb_3(AsO_4)_2$), lead tetra ethyl ($Pb(C_2H_5)_4$)

Maximum Permissible Concentrations in Air

The accepted maximum permissible concentration of lead in the air for an eight hour day is 1 5 milligrams per 10 cubic meters of air

Lead Absorption

Exposure to lead in any form usually provides some opportunity for it to gain entrance into the body The quantities may be small or they may be sufficient to cause fatal poisoning Between these two extremes varying amounts may be absorbed depending essentially upon the intensity and duration of the exposure and, to some extent upon the physical and chemical characteristics of the particular lead substances involved

Lead absorption should not be confused with lead poisoning These terms frequently are used interchangeably without regard to precise definition It is not unusual to hear mild cases of lead poisoning referred to as cases of *lead absorption* Lead absorption merely indicates the presence of lead in the body without implying anything as to how much is present whether the amounts are within normal limits or in excess of normal whether or not there are any clinical evidences of disease When absorption is sufficiently great, signs and symptoms begin to manifest themselves which may be collectively referred to as *lead poisoning* Consequently, when lead poisoning is present one is always

dealing with lead absorption but the reverse is not necessarily true Acute awareness of these distinctions when examining a patient is of greater practical value to the physician than is commonly realized It illuminates his clinical findings it indicates to him the type of laboratory data which will be most useful to him and it assists him in interpreting the one in terms of the other

It is useful to visualize lead absorption in a particular case as a more or less continuous physiological process characterized by special meta bolic responses on the part of the body to the lead which is being absorbed These metabolic activities can be kept under medical sur veillance and can be studied even in the absence of clinical disease Information thus obtained is indispensible for purposes of prevention Should lead poisoning subsequently develop this period of observation provides data of inestimable value for diagnosis and therapy

Fate of Lead in the Body

Lead is absorbed into the body primarily by inhalation of air con taining lead dust or lead vapors It may also enter the body by way of the gastrointestinal tract as a result of ingestion Only organic lead compounds such as tetra ethyl lead are absorbed through the skin in significant amounts[8]

Of the lead which is swallowed the larger part is not absorbed but passes through the gastrointestinal tract without injury to the body and is eliminated in the feces The remainder is absorbed into the portal circulation which carries it to the liver[9] Three things may happen to lead which reaches the liver 1) part of it is stored there 2) part is excreted into the feces by way of the gall bladder 3) a third part passes through the liver into the general circulation and is either stored in the bones or other tissues of the body or is excreted by the kidneys into the urine

Lead in the air which a worker breathes whether in the form of dust or vapor is inhaled and carried to the lungs From these it is absorbed directly into the general circulation Lead which is inhaled is far more dangerous therefore than that which is swallowed

After lead has been absorbed into the general circulation regardless of the precise portal of entry it is carried in the blood stream as the soluble dibasic phosphate to all parts of the body The liver spleen kidneys lungs and muscles are sites of primary storage Deposited in

the gums it gives rise to the familiar *lead line* Gradually, however, the lead is transferred for more permanent storage to the bones, first in the trabeculae and then in the cortex There it remains relatively inert in the form of the tribasic phosphate It is always subject, however, to possible mobilization at some future time as metabolic processes in the body become propitious

Table I indicates the general distribution of lead in human tissues in cases of plumbism

TABLE I

DISTRIBUTION OF LEAD IN HUMAN TISSUES IN PLUMBISM
(AUB FAIRHALL MINOT AND REZNIKOFF)[9]

	Case 1		Case 2		Case 3		Case 4	
	Con cent mg /	*Total mg*	*Con cent mg /*	*Total mg*	*Con cent mg /*	*Total mg*	*Con cent mg /*	*Total mg*
Liver	5.11	99	0.12	1.65	0.68	10.88	0	0
Kidney	1.00	0.97	0.35	0.94	.45	.84	0	0
Spleen	1.07	0.77	1.59	2 3	0	0	0	0
Pancreas	10.00	1.09	—	—	—	—	0	0
Heart	0.56	0.30	0.32	0.99	—	—	0	0
Lung	0.32	0.61	0 9	4.41	0	0	—	—
Cerebrum	0.36	2.91	0	0	0.22	3.20	—	—
Cerebellum and Medulla	0.6	0.65	0.49	0.71	0.30	—	—	—
Spinal Cord and Peripheral Nerves	—	—	—	—	—	—	—	—
Skeletal Muscle	—	—	—	—	—	—	—	—
Skeleton	15.30	195.8	4	80.0	7.16	800.0	2.17	243.0
Washed Gastrointestinal Tract	0.46	1.59	—	—	—	—	0	0
Blood	trace	—	0.27	—	—	—	—	—
Bile	trace	—	0	0	—	—	—	—

The metabolism of lead calcium and phosphorus are very closely interrelated Moderate amounts of calcium and phosphorus and small amounts of vitamin D in the diet tend to favor lead storage Larger amounts particularly of Vitamin D, favor mobilization[13] Thus it is possible to promote storage of lead or its mobilization by manipulation of the metabolic factors involved This very delicate equilibrium between lead storage and lead mobilization can be readily disturbed by many factors, including intercurrent infection changes in the acid base balance of the body and a variety of alterations in metabolic processes[11,1]

Lead excretion is primarily by way of the urine and feces Both absorbed and unabsorbed lead are to be found in the feces Lead in the urine however represents only lead which had been absorbed previously into the blood stream Maximum lead excretion may be anticipated during periods of active absorption but excretion may continue to a lesser degree for weeks or even months after absorption had ceased Should mobilization of stored lead occur at some future time even years later it will be evidenced by renewed lead excretion in the urine Small amounts of lead may be found in the urine of persons with no unusual lead exposure as previously indicated

It is fortunate that laboratory methods of considerable accuracy and refinement are now available for the study of lead absorption And new data are being developed as biochemical research continues Of special theoretical interest are studies which for example are throwing light upon the effects of lead upon pigment formation[8], or the effects of lead upon the oxygen consumption of tissue cells[15] These contributions are of primary interest however to research workers rather than to medical practitioners The present discussion will be limited therefore to those data which can be utilized by the practicing physician for the practical solution of medical problems presented by patients suffering from lead poisoning or for the prevention of lead poisoning in persons exposed to lead

Blood

Chemical analysis of whole blood for its lead content will reveal whether or not abnormal amounts had been absorbed recently Hematological studies will indicate the effects of lead absorption upon hematopoiesis Non specific alterations in blood chemistry such a hyperbilirubinemia[16] for example are of less value for practical purposes in the interpretation of lead absorption or the diagnosis of lead poisoning

Lead Content of Whole Blood — Small amounts of lead may be found in the blood of so-called normal individuals Found in excess of 0 07 milligrams per 100 grams however the possibility of an unusual lead exposure and lead absorption should be considered and investigation instituted Mobilization of previously stored lead also must be taken into account as possibly contributing to the total lead content of the blood

Since it is the concentration of soluble lead in the systemic circulation at any given time which is essentially responsible for the development of clinical lead poisoning quantitative determinations of the lead

content of whole blood are of unusual interest It is necessary, however, *in interpreting these findings, to take into account the interval* of time which had elapsed between lead exposure and the taking of the blood sample Obviously the longer the interval, the more opportunity will there have been for the removal of lead from the blood either by storage or excretion

The finding of abnormal amounts of lead in the blood, when interpreted in the light of these time relationships, is of great importance, but this is only a single finding in a complex medical syndrome For purposes of diagnosis it must be interpreted together with all of the other elements in the medical picture

Lead Anemia — Lead absorption produces a very characteristic blood dyscrasia Contrary to common belief, however, it is one in which stippled cells, though peculiarly characteristic of lead are neither pathognomonic, nor are they of sole interest All blood dyscrasias are a composite of many distinctive hematological characteristics which are of great interest individually but which can be interpreted only as a whole Lead anemia is no exception Here, as in all other blood dyscrasias abnormal cells tend to be thrown into the circulation only intermittently Repeated blood examinations thus are indicated in each case No single blood smear no single abnormal type of cell, not even the presence of stippled cells nor their precise number, can be depended upon per se to provide definitive information Stippling of the red cells (Fig 3) is peculiarly characteristic of lead poisoning, but stippled cells are found also in other blood dyscrasias and also occasionally in the blood of normal individuals When stippled cells are found in considerable numbers, one is dealing with a blood dyscrasia, and the possibility of lead poisoning must be considered always Whether or not the blood dyscrasia is due to lead is a question of differential diagnosis The problem here is no different from that presented by any other blood disease

The use of a so-called *basophilic aggregation test* has been suggested as an aid to diagnosis on the theory that clumping of the reticulum in immature red cells is an earlier and perhaps more reliable sign than stippling in lead poisoning[17] or lead absorption

Lead anemia is characterized essentially by the association of a relatively high red cell count and hemoglobin with disturbances in erythropoiesis out of all proportion to that found ordinarily in what appears on the surface to be a mild secondary anemia Even in lead poisoning the red cell count does not often drop below 4 million nor the hemoglobin below 80 per cent[18] though there are exceptions With this one

may find marked polychromatophilia many stippled cells occasional nucleated red cells and a considerable degree of poikilocytosis anisocytosis and crenation of red cells (Figs 1 and) Stippled cells (Fig 3) may be present in large numbers 800 to 1 000 per million erythrocytes[9]

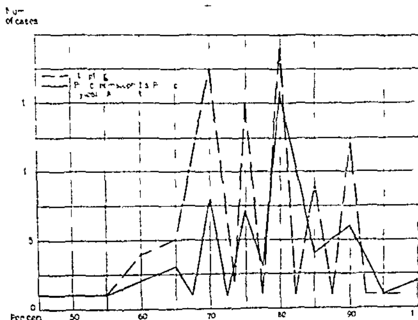


Fig 1 Showing the relation of the hemoglobin to the presence of stippling polychromatophilia poikilocytosis and anisocytosis[19]

On the other hand their presence in lesser amounts or even their absence in a single blood smear does not necessarily rule out lead anemia

Individually all of the abnormal cells including the stippled cells which may be found in the blood of a lead worker may be found also in other blood dyscrasias but in the latter the presence of such abnormal cells would be associated with a conspicuously greater drop in the red cell count and the hemoglobin Moreover the pallor of the lead worker being due to a neuromuscular constriction of the capillary circulation bears no direct relationship to the blood count or hemoglobin and is far more intense than would be found in any other blood disease where the number of red cells and hemoglobin have been reduced only so

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acteristic blood picture also may be completely absent The extent to which lead anemia will be manifest in classical form at any given examination will be influenced greatly by the intensity and duration of exposure to lead[1] the time which has elapsed between lead exposure and the onset of symptoms and the time which has elapsed between

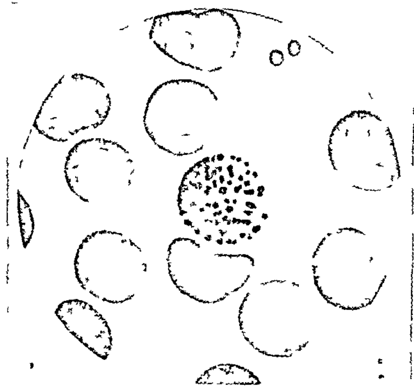


Fig 3 Stippling in lead anemia[18]

the onset of the illness and the present physical examination After exposure to lead has ceased blood abnormalities tend to disappear and hematopoietic function gradually returns to normal Thereafter only if there is subsequent mobilization of lead from previously stored deposits will there be any evidence in the blood smear that lead had at some previous time been absorbed into the body

slightly The association therefore of marked pallor with a seemingly mild secondary anemia as judged by the red cell count and hemoglobin accompanied by serious disturbances in hematopoiesis should immediately put one on notice to investigate the possibility of lead as the etiological factor in the case

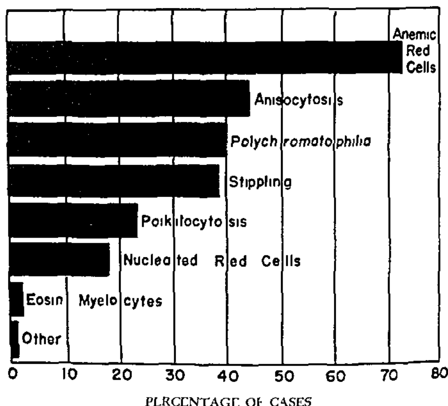


Fig Showing the relative prevalence of the various types of blood changes found in 238 cases[13]

Typical lead anemia may develop as a result of lead absorption even in the absence of clinical lead poisoning It is always an important danger signal indicating immediate need for further study of the patient In clinical lead poisoning lead anemia is a characteristic finding excepting under special circumstances In acute lead colic, for example, hematological abnormalities are prominent In an old case of multiple neuritis of long standing the blood smear may be perfectly normal When the body is completely overwhelmed as in acute encephalopathy, the char

tion of cases of suspected lead poisoning in communities with a high lead content in the drinking water. In the United States an interest in the porphyrins as an aid to the diagnosis and control of lead poisoning is just beginning to develop. Reports of recent experiences with this test have indicated thus far a somewhat limited usefulness. Active research work is in progress.[7, 1]

Types 1 and 3 coproporphyrins may be found in normal urine. They are found to be markedly increased not only in lead poisoning but in a variety of other conditions such as diseases of the liver, particularly when associated with jaundice, chronic alcoholism, infectious diseases such as pneumonia and poliomyelitis, and intoxications due to arsenic, sulphonamides, acetylsalicylic acid and a variety of commonly used pharmaceutical products. Intermittent increases are to be found in various anemias and leukemia. In a condition known as porphyria, which is believed to be congenital, 582 micrograms of type 1 coproporphyrins have been found in a twenty four hour specimen of urine and 147 milligrams of uroporphyrins in a single specimen of urine.[6]

There are various theories to explain the increase in urinary coproporphyrins in these many conditions. A metabolic disturbance involving increased synthesis and excretion is considered a possibility. In lead absorption and poisoning it is believed that the normal combination of protoporphyrin with iron to form hemoglobin may be interfered with, the uncombined porphyrins being converted into coproporphyrin and excreted in the urine.[7] A possible impairment in hepatic excretory function has been suggested as an explanation for the increase in coproporphyrins in the urine in hepatic diseases. Since the liver is the great detoxifying organ in the body, it would be interesting to know whether or not in lead poisoning both mechanisms combine to produce the end result.

Obviously too little is known about the porphyrins at the present time, particularly the relation of urinary porphyrins to total porphyrin excretion as measured by accurate quantitative methods. For additional information in regard to porphyrin see chap. IX A in Vol. IV of Oxford Medicine.

Feces

Lead in the feces may represent both absorbed and unabsorbed lead and there is no way of distinguishing between them. Laboratory analysis of the feces for lead therefore does not provide data comparable in

Urine

The most important information to be obtained from an examination of the urine is accurate quantitative data as to its lead content. Since whatever lead appears in the urine is excreted from the systemic circulation, it is an excellent index of lead absorption. Here again mobilization of lead from previously stored deposits, when it occurs, will contribute to the lead content of the urine.

Lead Content of Urine.—The urine normally contains extremely small amounts of lead. When its lead content is found to be in excess of 0.1 milligram per liter, however, investigation of possible lead exposure and lead absorption is indicated. Assurance that the urine sample has not been contaminated with lead is an obvious essential.

The extent to which the excretion of lead in the urine fluctuates from specimen to specimen and from day to day and the factors underlying this phenomenon have been mentioned already. Under the circumstances in a given patient a large pooled specimen of urine, at least 1,000 c.c., will provide far more useful information than any single specimen. Repeated examinations of the urine are desirable.

Accurate and reliable quantitative data on urinary lead is an invaluable aid to diagnosis. Their great value lies not alone in the precise number of milligrams present but rather in the fact that, when such data are considered in connection with the lead content of the blood, they contribute to an understanding of current inter-relationships between exposure, absorption and excretion. They materially assist, thereby, in the interpretation of hematological and clinical findings in a suspected case of lead poisoning.

After exposure to lead has ceased, the lead content of the urine gradually returns to normal. It is important here, therefore, as in dealing with other laboratory data, to give due consideration to the many time relationships involved, particularly the interval which had elapsed between exposure to lead and the collection of the urine sample.

The practical application of data on urinary lead to the industrial control of lead poisoning is of great importance. It will be discussed under PREVENTION.

Porphyrinuria.—An increased excretion of porphyrins (coproporphyrins type 3) in the urine and feces has been found in lead absorption and poisoning. In Europe semi-quantitative tests for porphyrins in the urine have been done for many years on lead workers. More recently in Sweden this test was used with apparently good effect for the detec-

Lead deposits are found concentrated primarily in long and flat bones The ends of long bones contain more lead than the shafts The tibia and fibula contain more than the ribs or the vertebrae Flat bones such as the scapula or the pelvis have greater lead deposits than tubular bones In the teeth lead is deposited primarily in the dentine and the roots No relationship however has been demonstrated between lead deposits in the teeth and dental caries

Lead appears to have a special affinity for the ends of growing bones where, even at lower levels of lead exposure and absorption it is stored in larger amounts than in fully developed bones Also once deposited there in the young it appears to be more stable than in the adult Lead shadows observed on x ray in the bones of infants and growing children therefore assume unusual significance whereas bone shadows in adults throw no significant light upon lead absorption

The deposition of lead in the bones may be seen as bands of increased density at the ends of long bones and at the margins of flat ones[3] They present linear rings of increased density in the ossification centers of the epiphyseal cartilages and appear as a series of transverse lines in the diaphyses just below the epiphyses Bone shadow bands are broader and of greater density where growth is most rapid as for example at the lower ends of the radius ulna and femur the upper end of the humerus and at both ends of the tibia and fibula The age of the child as well as intensity and duration of exposure to lead will determine the amount of lead which is stored and the appearance of the x ray shadows In the small bones of infants it is possible to see shadows cast by amounts of lead too small to be visualized in the larger bones of older children Because of their appearance and distribution x ray shadows due to lead can be confused very easily with shadows of increased density produced by healing rickets particularly when the healing process is rapid

Reproduction

Lack of quantitative data makes it difficult to evaluate relationships between lead absorption and the reproductive cycle of women working in the lead industries Most of the case reports go back many years to a time when exposure to lead in industry was of quite a different order of magnitude from what it is today and when present day chemical techniques were not available or not in common use to evaluate the extent of the lead exposure or absorption Nevertheless the clinical

usefulness with that obtained from the blood or urine However, the finding of abnormally large amounts in the feces suggests the need to investigate the patient's lead exposure immediately preceding the examination

Where data as to total excretion of lead is desired as in deleading procedures for example the lead content of the feces must be measured Similarly, if data as to total porphyrin excretion are desired quantitative analysis of the feces as well as of the urine is necessary

Reliable data as to total excretion usually cannot be obtained unless the patient is hospitalized

Spinal Fluid

Lead has been found in the spinal fluid of normal individuals with no unusual lead exposure, it has been found in the spinal fluid of persons suffering from diseases of the central nervous system and it has been found in lead absorption and lead poisoning where it appears to bear no quantitative relationship either to the lead content of the blood or to the presence or absence of neurological disease[11]

Lead found in the spinal fluid therefore is difficult of interpretation In a patient, suspected of having lead poisoning the mere presence of lead in the spinal fluid does not of itself clinch the diagnosis Similarly when studying any obscure neurological condition, the finding of lead in the spinal fluid does not indicate that lead was necessarily the etiological agent All other evidences if any of lead absorption and lead intoxication must be investigated carefully and the whole clinical syndrome evaluated together

Lead in the Bones

Storage of lead in the bones during active absorption and in the period immediately following it already has been discussed and the close parallelism pointed out between the metabolism of lead and calcium in the body particularly in relation to lead storage and mobilization Actually the major part of all absorbed lead which is not excreted is stored in the solid portions of the bones especially in the epiphyses first in the trabeculae and secondarily in the cortex It can be demonstrated histologically to be deposited largely in the endostium where it may be found in occasional proximity to capillary walls[10] Very little lead is stored in the bone marrow and none, apparently in cartilage

tion,) a group in which gastrointestinal disturbances predominate including acute lead colic 3) one having predominately neuromuscular disturbances including peripheral neuritis and wrist drop 4) one characterized by disturbances of the central nervous system including lead encephalopathy and 5) childhood lead poisoning

Actually most persons exposed to lead under the more or less controlled conditions which prevail at the present time in the larger industrial countries are mixed cases of a relatively mild character

Prodromal Syndrome

General prodromal symptoms may include one or more of the following loss of appetite so called metallic taste constipation or other mild gastrointestinal disturbances lassitude weakness insomnia headaches and nervous irritability muscle and joint pains Physical examination at this point usually will reveal a poorly nourished individual with a characteristic lead pallor having no relation to any blood dyscrasia Varying degrees of tremor particularly a fine tremor of the fingers tongue and eyelids may be seen Attention has been called particularly to the fact that on light stroking a contraction of the facial muscles may be elicited[35]

Lead Line — A lead line in the gums may or may not be present at this time When present however it indicates absorption and storage of lead in the gums Per se it never indicates lead intoxication nor does its absence rule out this condition It may persist for several months after exposure to lead had ceased

Lines of increased density in the bones of adults sometimes mistakenly referred to as a lead line are without diagnostic significance in adult lead poisoning

The true lead line in the gums is composed of fine particles of bluish black deposits of lead sulphide within the substance of the gums For that reason it cannot be scraped or brushed off It is characteristically found to be associated with teeth which are in poor condition and must be differentiated from the bluish discoloration of the gums due to chronic gingivitis The lead line is observed less often in persons with healthy gums Edentulous individuals rarely show it On the other hand the normal pigmentation of the gums in dark skinned individuals may be very deceptive

A strong light and a good magnifying glass greatly assist in its iden

experience, which has accumulated over the years, together with more recent laboratory data obtained from experimental work on animals all tend to support the belief that, in sufficient amounts, such exposure may be responsible for disturbances in menstruation, an increase in the frequency of sterility abortions and stillbirths and a higher infant mortality

These phenomena are interpreted and explained in the light of what is known about the effects of lead upon the hematopoietic system and its tendency to produce spasm of smooth muscle Lead induced spasm of the uterine muscle, analogous to intestinal spasm in lead colic is believed to be a contributing factor in the high incidence of abortion Studies of the influence of lead upon abnormal cell growth[68] have indicated that lead causes injury to the fetus and subsequent abortion through its action on the chorionic epithelium Lead has been shown to pass from maternal to fetal circulation, and it is believed that fetal tissues are highly susceptible to lead

There is reason to question a belief widely accepted in the past to the effect that leaded males also have a tendency toward sterility and that they produce weaker and undersized offspring Under modern conditions of exposure to lead in industry and on the basis of experimental evidence this would seem doubtful Where industrial exposure to lead is extremely high however, and workers bring large quantities of lead dust back home in their work clothes it is conceivable that there may be significant direct exposure of mothers and babies to accumulations of such dust particularly where workers are poorly housed and meticulous housekeeping is impracticable

Clinical Lead Poisoning

Since absorbed lead is carried in the blood stream to all parts of the body a great diversity of clinical manifestations may result These will depend very largely upon the tissues or organs particularly involved in any given case and may not necessarily differ essentially from other organic disease of these same tissues or organs Difficulties in differential diagnosis are inherent in this situation

In order to facilitate an understanding of this peculiarly elusive disease it is profitable to think of it in terms of five fundamental and characteristic clinical syndromes 1) prodromal symptoms and signs which are rather undifferentiated manifestations of early lead intoxica

tion, 2) a group in which gastrointestinal disturbances predominate including acute lead colic 3) one having predominately neuromuscular disturbances including peripheral neuritis and wrist drop 4) one characterized by disturbances of the central nervous system including lead encephalopathy and 5) childhood lead poisoning

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tification. It is well, however, to bear in mind that bismuth and other metals may also cause a dark sulphide deposit in the gums closely resembling the lead line.

Prodromal symptoms and signs of early lead intoxication thus tend to be very general and relatively undifferentiated in character. They may be found in a variety of other conditions. However, certain combinations immediately suggest the possibility of lead poisoning and the need for further investigation. Typical of this, for example, is the combination of constipation, pallor unrelated to anemia and nervous irritability, with or without a lead line in the gums.

In a lead worker even such a common complaint as chronic constipation should be a signal for prompt and complete investigation. In disposing of the case by prescribing a cathartic, which is often done, valuable time may be lost and the opportunity to prevent an attack of lead colic forfeited. Particularly, if the constipation is persistent or progressive, a careful occupational and clinical history are immediately indicated together with a thorough clinical examination of the patient and laboratory studies of blood and urine. Progression of symptoms is of special significance in these cases. Trends contribute greatly to an interpretation of the medical findings.

Gastrointestinal Syndrome

The precise nature of the early prodromal signs and symptoms presented by the patient will not necessarily indicate the ultimate clinical pattern or course which the disease will follow if exposure to lead continues. However, where persistent constipation and other gastrointestinal disturbances predominate, one can under those circumstances more often than not anticipate the onset of an attack of acute lead colic.

Familiar precursors of acute lead colic are nausea and vomiting. During this period the patient often complains of heaviness or a feeling of weight in the umbilicus in addition to some of the prodromal symptoms already mentioned. Physical examination at this stage usually will reveal the characteristic lead pallor, tremor and perhaps a lead line. On palpation of the abdomen fecal masses may be felt and some tenderness elicited along the course of the colon.

Acute Lead Colic.—This is characterized by spasms of intense abdominal pain in which the patient is found in a cold sweat with marked pallor, writhing or doubled up. Acute surgical abdomen imme-

diately suggests itself Indeed the case of lead colic which has been operated upon mistakenly for acute appendicitis is a classic illustration However there are important differences In lead colic particularly in the interval between spasms the pain tends to be relieved by pressure and there is an absence of that board like rigidity of the abdomen which characterizes surgical abdomen There is no rebound tenderness and little if any radiation of the pain The rise in temperature and the leukocytosis characteristic of acute infectious processes also are absent The pulse is slow Jaundice is rare though a yellowish tint to the sclerae may be observed where there has been unusual blood destruction More or less discrete doughy abdominal masses representing intestinal coils separated by bands of constriction may be visible and may suggest ileus

These characteristic differences in the clinical picture should in general make the differential diagnosis from surgical conditions of the abdomen not too difficult Nevertheless acute appendicitis cholecystitis or lithiasis renal colic perforated gastric or duodenal ulcer intestinal obstruction and the like must be considered and carefully ruled out in each and every case quite regardless of known exposure to lead on the part of the patient

Interpretation of physical signs and symptoms in the light of the underlying and characteristic physiological mechanisms which have given rise to them is axiomatic for good differential diagnosis In the case of acute lead colic the characteristic mechanism is the specific action of lead upon smooth muscle causing it to go into spasm Interpreted with this in mind the findings on physical examination are greatly clarified and accurate differential diagnosis facilitated

Since intravenous administration of calcium gluconate promptly relieves lead colic this provides a most valuable aid to differential diagnosis when in doubt

Lead colic usually will subside within a week or ten days and complete recovery is the rule However residual symptoms may persist for many weeks with poor appetite constipation or recurrent abdominal pain Backache and general weakness are frequent complaints during this period

Neuromuscular Syndrome

Although gastrointestinal and other complaints are not absent in this clinical syndrome the predominant elements are weakness or paralyses

of extensor muscle groups, particularly those of the forearms and the hands. There may be arthralgia, myalgia and stiffness of other muscle groups which may be mistaken for rheumatism. One is especially impressed with the discrepancy between the muscular development of the patient and his lack of muscle strength. Headaches, dizziness and insomnia are more prominent than in the gastrointestinal group.

Paresthesias may be observed during this prodromal period. Extensor weakness usually precedes true palsy by some weeks. With prompt and proper management of the case, therefore, paralyses may be prevented. After they have developed, however, muscle atrophy usually is progressive and may be associated with some cyanosis and trophic changes. It is especially characterized by reduction or loss of response to electrical stimulation. Thermal, tactile and vibratory sensitivity usually are impaired. Reflexes are inconstant, but extensor reflexes usually are absent.

Muscle fatigue appears to play a determining role in the localization of lead palsies. This has been confirmed experimentally and the theory has been advanced that the cause lies in metabolic disturbances within the muscles[9]. Interference of lead with the processes of resynthesis of phosphocreatine has been suggested as a possible explanation for these metabolic disturbances[11].

It is characteristic of the lead palsies that the muscles involved usually are those which are functionally related to one another rather than those related by a common nerve supply. So in a given case all of the muscles found to be affected are not necessarily supplied by the same nerve or nerves and conversely, the muscles supplied by a single nerve may not all be involved.

This characteristic selectivity of lead for muscles which are most used and thus most subject to fatigue is well illustrated by the fact that brush painters using lead paint have been observed to develop wrist drop predominantly; those who apply the paint above their heads or persons who do heavy lifting or carrying tend to develop paralyses of the shoulder muscles; children and laborers who use their legs more than their hands tend to develop ankle drop and so forth. When the work is of a more varied character, paralyses are apt to be correspondingly widespread in their distribution. Lead paralyses are not mutually exclusive as to site, and various combinations may be found in a given case.

The characteristic paralyses due to lead usually are considered under the following categories in order of frequency:

1) *Antebrachial Type* (Wrist Drop) — This is the most common of the lead palsies and involves primarily the extensors of the wrist and fingers but not the flexors or the supinator longus Of considerable interest is the characteristic absence of involvement of the supinator longus even though it has the same nerve supply as the affected muscles (see Fig 4)

Beginning with the extensor communis digitorum the paralysis may be confined to this muscle or it may progress first to the extensors of the index and fourth fingers then to the long extensor of the thumb the extensors of the wrist the interosseous muscles The long abductors of the thumb are seldom involved and usually come last Very occasionally the interosseous muscles may become involved early

2) *Brachial Type* — This involves the deltoid primarily either alone or together with the biceps the brachialis anticus and the supinator longus (Fig 5) Only occasionally are other muscles in this area affected Functional limitations of motion are dependent upon the relative involvement of the several muscles and its extent

3) *Aran Duchenne Type* — Here the thenar and hypothenar eminences are characteristically affected either alone or in conjunction with the interosseous muscles Muscle atrophy may be very extensive in these cases Wrist drop frequently is present

4) *Peroneal Type* — This type of paralysis characterized by ankle drop rather than wrist drop is found more commonly in children than in adults The peroneal muscles are involved primarily together with the extensors of the feet and toes The tibialis anticus usually escapes The gastrocnemious is affected rarely Peculiarities of posture may develop and limitations of motion which are determined in any given case by the particular muscles affected and the extent to which impairment of function has disturbed normal muscle balance

5) *Laryngeal Type* — This is extremely rare When it does occur however it results in aphonia or inspiratory dyspnea depending upon whether abductor and adductor muscles are involved The transverse and oblique arytenoid muscles also may become paralyzed[11]

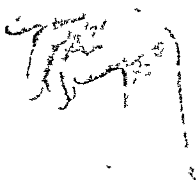
6) *Miscellaneous* — Other more widely distributed paralyses have been observed and reported paralyses of the back for example of the limbs and even the intercostal muscles and the diaphragm in some cases Where these latter muscles become involved death may occur from respiratory failure Cases closely resembling polyneuritis have been reported also paralysis of the muscles of the eyeball especially the



2



3



4



Fig 4 Development of wrist drop in a lead worker[41] (pictures from the private collection of Dr Ludwig Teleky)

external rectus Involvement of the optic abducens and facial nerves usually are to be found only in association with lead encephalopathy Muscles of the head and neck appear to escape injury

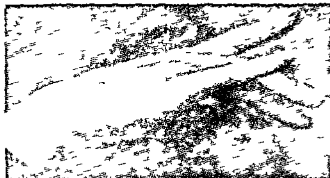
The physical examination of the patient should be especially directed toward an evaluation of motor and sensory disturbances measurements of muscle weakness and muscle atrophy if present and a careful evalua



Fig 5 — Lead palsy involving the shoulder girdle as well as the arm (Courtesy of Joseph C Aub)

tion of mental status The eyes should be examined with great care particularly for weakness of the extrinsic muscles retinal hemorrhages or optic neuritis

Neuromuscular involvement due to lead must be differentiated from peripheral neuritis due to a great variety of infectious and toxic agents



2



3 4

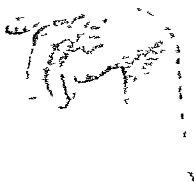




Fig. 4 Development of wrist drop in a lead worker[41] (pictures from the private collection of Dr Ludwig Teleky)

of lead cases described where there is exposure to smaller amounts of lead for longer periods of time[8, 44, 49] In acute encephalopathy extremely large amounts of lead will be found in the urine indicating the severity of the exposure and the large amounts of lead which had recently been absorbed On the other hand stippled cells and evidences of a blood dyscrasia usually are absent because too short a time had elapsed for the hematopoietic system to respond characteristically to the rapid lead absorption

Visual disturbances are associated especially with lead encephalopathy Characteristic physical findings are pallor of the optic disc retinal hemorrhages weakness of the extra ocular muscles and in some cases optic neuritis which usually is bilateral and may be intra ocular or retrobulbar

The spinal fluid usually is under increased pressure In children particularly there may be an increase in the cellular elements of the spinal fluid and an increase in globulin[11]

Death is believed to be due to cerebral edema tissue starvation dehydration and exhaustion[9] If it does not occur in the first few days recovery may be complete in a matter of weeks or months Permanent sequelae however particularly permanent mental deterioration are always a possibility (Fig 6) In children complete recovery is rare



Fig 6 Permanent mental deterioration following lead encephalitis[41] (picture from the private collection of Dr Ludwig Teleky)

These cases must be differentiated from many other diseases of the central nervous system particularly neurosyphilis cerebral arteriosclerosis and encephalitis due to infections and toxic agents other than lead Acute carbon monoxide poisoning should be considered always In cases with acute onset the distinguishing characteristics are 1) a history of extreme lead exposure at the time of onset 2) unusually large amounts of lead in the blood and urine and 3) the absence of stippling

as well as from that due to malnutrition Distinguishing characteristics of lead palsies are 1) they are painless, 2) they are essentially motor, 3) they are limited to the extensor muscles, 4) the sites of involvement are remarkably constant, 5) the muscles most involved usually are the ones most used in the course of the day's work, and 6) there is a history of significant exposure to lead[40]

In general a more intensive exposure to lead over a longer period of time is required to produce neuromuscular involvement than to produce lead colic Palsies tend to develop after one or more attacks of colic in a worker who continues his work with lead[42]

Complete recovery, even from paralysis is entirely possible, though it may take a long time one or two years or even longer perhaps The longer-standing the condition the more permanent will it tend to become Immediate removal from further exposure to lead is a matter of the greatest urgency in these cases

Involvement of Central Nervous System

Exposure to massive doses of inorganic lead, sufficient to cause severe cerebral intoxication has been practically eliminated under modern conditions of industrial exposure to lead At the present time the rare cases of this type, which occur, are more characteristically associated with exposure to organic lead compounds particularly tetraethyl lead Children appear to be far more susceptible than adults to involvement of the central nervous system in lead poisoning and are less apt to show complete recovery[43,44,45,46]

Acute Encephalopathy — Pathologically this condition is looked upon as a meningoencephalitis actually a lead encephalitis[40,47] Its onset may be sudden with collapse or with extreme excitation confusion deep stupor, with or without convulsions The coma, which ensues may result fatally, or there may be recovery Less acute cases which show headache, dizziness confusion insomnia or somnolence, may go on to permanent mental impairment or recovery Gastrointestinal disturbances are less commonly associated with this group of lead cases than with any of the others

The syndrome develops rapidly in response to an overwhelming dosage of lead such as may result particularly from exposure to organic lead compounds including tetraethyl lead The response of the body is strikingly different therefore from that found in the other groups

Diagnosis

The diagnosis of lead poisoning rests upon three pillars 1) Evidence that there has been significant exposure to lead This is obtained primarily from the occupational history given by the patient Whenever practicable the occupational exposure should be verified by a field investigation 2) Evidence of clinical lead poisoning This derives from the physical examination of the patient and a careful differential diagnosis 3) Evidence of lead absorption in excess of what is considered normal This is obtained from laboratory studies of blood and urine and in addition in growing children only x ray studies of the bones

The final diagnosis in each and every case is a synthesis of the data obtained from all three sources the lead exposure the clinical picture and the laboratory findings Each finding in each of these categories ultimately must be evaluated and interpreted in the light of the whole picture

Evidence of Significant Exposure to Lead

Occupational History — Physicians find the taking of a detailed occupational history an unwelcome chore This is due in part to lack of familiarity with it in medical school and in part to the fact that often it appears futile The patient does not necessarily remember to recount all aspects of his many jobs over the years and the practicing physician does not understand enough about the technology of the industries involved to ask pertinent questions To many physicians the mere fact that a patient is working with lead clinches a diagnosis of lead poisoning On the other hand the fact that his patiemt reports that no other worker in the plant is suffering from a similar medical condition causes many physicians to dismiss the case as non occupational Needless to say both of these assumptions are without foundation

A further difficulty confronting the physician in getting a realistic occupational history is the fact that exposure to lead in industry tends to be a long drawn out affair covering a great many years with periods in between perhaps when there was no lead exposure whatever While starting with the present occupation therefore it is necessary to go back to each previous occupation in turn and to inquire painstakingly as to the nature intensity and duration of each previous exposure to lead

The occupational history though tedious and at times difficult to obtain with accuracy is nevertheless indispensable to the physician who

and other hematological changes ordinarily characteristic of lead poisoning

Childhood Lead Poisoning

Lead poisoning in infants and children is a disease frequently characterized by convulsions It has a very high rate of mortality Since convulsions in infancy are not uncommonly associated with nutritional deficiencies however a careful history and physical examination are essential in each case, particularly an evaluation of the nutritional status of the child In addition, factual data must be sought as to whether or not there had been any unusual exposure to lead Convulsions associated with rickets may be especially confusing because they may be associated with bone shadows on x-ray which closely resemble the bone shadows seen in childhood lead poisoning These have already been described in the section on LEAD ABSORPTION

X-ray of the bones in infants and growing children, when properly interpreted provides an invaluable aid to diagnosis Indeed absence of characteristic bone shadows should throw considerable doubt on a diagnosis of lead poisoning in these cases although in and of itself their absence does not definitely rule out such a possibility

Anemia is far more marked in childhood lead poisoning than in adults The type of anemia however is essentially the same as is also the general hematological picture Increased lead in blood and urine is found in children as in adults and the normal standards appear to be about the same

Lead encephalopathy in infants is associated with high fever, but there is no increase in the white blood cells or other evidences of infection to account for the fever The spinal fluid is under increased pressure, and papillary edema is observed There is an increase in the globulin of the spinal fluid without any change in the cell count Glycosuria is a characteristic finding The clinical course in the hospital during the first few days is of the greatest importance in throwing light upon the diagnosis A child entering with convulsions and fever due to lead will not be seen running around the ward in a few days well on the road to recovery Babies and children suffering from lead encephalopathy are desperately ill The mortality is high, and those who recover usually remain mentally retarded thereafter

Field Investigations — When the patient's exposure to lead has been recent a visit to the plant (or to the home in the case of a child) is a first essential whenever this is at all practicable Past exposures to lead do not however, lend themselves as readily to verification by investigations on the spot Even when the type of work which the patient did still is being carried out and a visit to the plant still is possible one usually will have to assume a greater exposure to lead in the past than that found at the time of the visit years later Lead exposures as found today are rarely representatives of those of a decade or more ago because of major technological developments and the effectiveness of engineering controls

As a practical matter a visit to a plant by a physician is not only time consuming, but it is apt to be unproductive even when he succeeds in getting the complete cooperation of management in showing him everything he came to see for it takes a skilled observer to understand technical plant operations and proper evaluation of the intensity of the exposure, i e, dosage per working day usually is possible only on the basis of quantitative chemical air analyses which are quite out of the field of the medical man However practicing physicians can turn for this type of technical data to Divisions of Industrial Hygiene in State or Federal Health and Labor Departments These services are available in many countries and usually can be had without charge Inquiries from physicians always receive prompt attention

Special experience may be required however for the interpretation of a report coming from such an agency for it may not be a medical report at all Instead it may be a statement from the chemical laboratory as to the average amount of lead found in the air of the workroom at the breathing level of the worker (the patient) in terms of milligrams of lead per ten cubic meters of air Ten cubic meters are used as the standard because it is estimated that in an eight hour day a worker will have inhaled approximately that volume of air The accepted maximum permissible limit of 1 5 milligrams of lead per ten cubic meters of air represents what has come to be regarded as a generally safe dose for the average person

A statement as to average lead concentration usually represents the result of a chemical analysis of a sample of air taken over a period of time perhaps an hour or more It does not provide information as to surges i e exposure to very much higher concentrations of lead in the air intermittently or perhaps for very short periods of time These surges if plotted may resemble a septic temperature chart The average

is studying a case of suspected lead poisoning A history of exposure to lead does not, however, in and of itself, make a diagnosis of lead poisoning It is entirely possible to work with lead and not contract lead poisoning Conversely, it is conceivable that a patient may be suffering from lead poisoning even though the physician has not succeeded in locating the source of the lead exposure In the absence of evidence that there has been a significant exposure to lead, however, a diagnosis of lead poisoning is open to serious questions and the medical findings upon which such a diagnosis has been based should be very carefully re-evaluated

An occupational history form, such as the following, may be of assistance in developing the type of information required

OCCUPATIONAL HISTORY FORM

Name of Patient M F

Address

Age at Commencing Work Present Age

OCCUPATIONS

(List in chronological order)

Name of Plant	Address	Product Manufactured	Precise Job There	Time Employed
1) Present occupation				
2) Each preceding occupation				
3)				
4)				

CHECK LIST BY CHEMICAL COMPOSITION

Chemical Designation		Industries	Occupations	Years in Each
Metallic Lead or Alloys	Lead Compounds			

Note One may if one desires break down these items as information becomes available with reference to specific metals in lead alloys or specific formulae of lead compounds

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values, as given, flatten out these curves into a straight line which is of value only if properly understood Further inquiry as to surges may be important therefore in getting a realistic concept of the occupational exposure of a given patient A low average may give a false impression of the true exposure and the true hazard

Another matter to be considered is the fact that there are certain types of lead exposures which cannot be evaluated by chemical analysis of air samples The repair man for example who from time to time has to climb into a drum used to process lead compounds in order to clean it out or recondition it is apt to have an extremely heavy exposure unless provided with a proper respirator and other personal protective equipment The extent of the patient s protection in certain special occupations involving peculiarly heavy exposures to lead dust or fumes even if for very short periods of time is therefore a necessary subject of inquiry in evaluating the occupational exposure An odd job such as this may not be the patient s regular work and he may even forget to mention it in giving his occupational history

Evidences of Clinical Lead Poisoning

In an occupational disease such as lead poisoning which is characterized generally speaking, by exposure to relatively low concentrations of lead for very long periods of time one is dealing with cumulative absorption which presents difficult diagnostic problems The patient is not necessarily acutely ill with colic His symptoms of constipation headache, nervousness or insomnia are in no way pathognomonic of lead poisoning or of any other specific clinical disease entity Perhaps he has come to the doctor's office with an infection in one of his toes and the examining physician observes that he has a wrist drop The wrist drop is an old story, as far as the patient is concerned, and he has not come to be treated for it What about lead poisoning in such a case? Why are there no stippled cells in his blood and no lead in his urine?

A medical understanding of such a case is not acquired by checking over and comparing the symptoms, physical signs and laboratory findings listed in text books with those presented by the patient It lies rather in trying to understand the dynamics of the situation Lead is absorbed into the body some of it is stored, some is excreted TIME is an important factor not only as it relates to duration of exposure but to the length of time which may have elapsed since exposure had ceased

The intensity of exposure in relation to time is important also In other words what one finds on physical examination is the resultant of a series of biochemical and physiological responses on the part of the body *over a period of time* to absorption into the body from time to time of varying amounts of lead

The man with the wrist drop above referred to, may or may not be found to have lead in his urine at a given physical examination Whether he does or does not has very little if anything to do with the wrist drop which probably developed years before Lead found in his urine at this stage gives information primarily as to the extent of his present lead exposure or absorption if any He has probably not been working with lead for years because of the wrist drop in which case one would not expect to find other signs of lead intoxication or abnormal amounts of lead in his urine at this late date On the other hand his wrist drop may never have been due to lead in the first place This requires investigation of his occupation at the time the wrist drop developed Investigation of the extent of lead exposure in his present occupation will not necessarily provide the answer

Differential Diagnosis — The clinical manifestations of lead poisoning and associated laboratory evidences of lead absorption have been described in some detail in the previous sections Points of differential diagnosis were considered in relation to each of these typical findings Since no one of them is pathognomonic for lead poisoning however each must be evaluated painstakingly in terms of all other diseases presenting similar clinical findings This is the classical procedure in all medical diagnosis and should not require special mention here The fact remains however that cases of suspected lead poisoning often fail to benefit from the type of comprehensive medical examination given other patients for purposes of differential diagnosis As a result non occupational diseases in a lead worker are often overlooked

It is the older worker who presents some of the most difficult problems the man who has spent many years of his life working with lead either continuously or intermittently For in the course of a long life many pathological and functional changes have occurred in various tissues or organs of his body These the physician is generally quite capable of evaluating medically However in the case of a lead worker he finds himself put to it all along the line to dissociate those elements in the clinical picture which properly may be attributed to the lead from those which may be due to other causes This is a major stumbling block and here a careful and thorough clinical history of the patient

will throw valuable light upon the findings on physical examination and help to rule out non occupational diseases or establish their presence

That prolonged exposure to lead accelerates the development of arteriosclerosis or chronic nephritis is an old medical concept which has not been confirmed by more recent work[0] On the other hand there is some data pointing to an association of hypertension with exposure to lead presumably not, however, on an arteriosclerotic basis[41]

The finding of such an obscure neurological condition as multiple sclerosis in a lead worker always gives rise to speculation as to the possibility of causal relation Cases in this category are reported periodically in the literature as due to lead absorption, particularly when lead is found in the spinal fluid Unfortunately however there are very little data available either as to the general etiology of these conditions or the role played by lead in their production That the mere presence of lead in the spinal fluid is inconclusive has been pointed out already No opinion unfortunately is possible at the present time with reference to causal relation in these cases

However whenever one is dealing with any obscure clinical disease entity regardless of what it is the medical picture as a whole must show some concrete evidence that there had been significant lead exposure, lead absorption or lead intoxication before lead can be considered as a possible etiological factor There must also be some pertinent relationship in time to the onset of the particular disease in question One cannot assume that because an obscure disease has occurred in a lead worker that it is necessarily due to lead

Individual Susceptibility — There are marked differences in individual susceptibility to lead as there are to other toxic agents both in and out of industry While no satisfactory scientific explanation is as yet available the existence of this phenomenon is strikingly evident In the field of epidemiology it is a familiar experience that in every epidemic certain individuals succumb to the disease while others do not

In the industrial field an important contribution along these lines may be in the making as a result of recent experimental work with toxic hepatitis Here it has been shown that the liver can, to some extent be protected against toxic doses of hepatotoxic agents such as carbon tetrachloride or chloroform for example by the administration of sulphur-containing aminoacids particularly methionine[4] It has been established also that alcohol and vitamin deficiencies especially a deficiency in vitamin C, appear to increase susceptibility to certain toxic chemicals[55]

Thus biochemical and metabolic differences between individuals may play determining roles.

Whatever the cause, these differences in individual susceptibility do exist and must be taken into account for purposes of diagnosis. Each case of lead poisoning must be examined on its own merits and cannot be evaluated in the light of whether or not the patient's co-workers have or have not contracted this disease also.

In plant medical surveys, undertaken for purposes of control and prevention, where the incidence of lead absorption or lead poisoning in a particular department provides a basis for interpretation of the adequacy of the control measures employed, differences in individual susceptibility are not pertinent to the purposes of the survey and can be disregarded. It is necessary, however, to distinguish between group data used for prevention and those which are required for a correct diagnosis in the case of a particular worker. The worker with unusual susceptibility may not be important statistically speaking, and the fact that he is suffering from lead poisoning does not necessarily indicate that industrial controls are inadequate. Nevertheless, if he has lead poisoning, this fact must be discovered promptly so that he may receive proper medical care.

Laboratory Evidence of Significant Lead Absorption

Laboratory evidence of lead absorption in excess of what is found in so called normal individuals is the third pillar upon which a diagnosis of lead poisoning rests. It is important at the outset, therefore, to have clearly in mind what the accepted normal standards are.

Normal Standards.[20, 3] — *Urine*. — Lead in the urine in excess of 0.1 milligram per liter of urine indicates an excretion of lead above that which one would ordinarily expect to find in a normal individual.

Feces. — Lead in the feces in excess of 0.50 milligram per gram of ash may be regarded as, in general, higher than normal.

Blood. — Lead in excess of 0.07 milligram per 100 grams of whole blood may be regarded as, in general, higher than normal.

The microscopic blood picture, including stippling of the red cells, must be studied as a whole for proper interpretation (see Lead Anemia).

Lead Exposure. — 1.5 milligrams per 10 cubic meters of air is regarded as the upper limit of safety for continuous exposure to lead in the workroom during an eight hour day.

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Laboratory Investigation — In each case of suspected lead poisoning the laboratory investigation should include as a minimum, 1) quantitative chemical analyses of the blood and urine for their lead content, 2) hematological studies not only for the presence of stippled cells but for all evidences of a blood dyscrasia characteristic of lead poisoning and 3) x-rays of the bones in the case of infants and growing children Bone shadows in adults have no significance in the diagnosis of lead poisoning

Lead found in the feces represents both absorbed and unabsorbed lead and the one cannot be differentiated quantitatively from the other For that reason determinations of lead in the feces are important only when total lead excretion is being investigated as in de leading therapy or in studies of total porphyrin excretions for example Total lead excretion can only be studied if the patient is in the hospital under constant medical surveillance

The collection of specimens of biological materials such as blood urine or feces for chemical analysis should be supervised or controlled carefully to prevent contamination with lead either from hands clothing glassware etc Similarly, in the laboratory extreme care must be exercised to prevent contamination from laboratory reagents and glassware

Only standard quantitative chemical methods should be employed, and analyses should be carried out by reliable and experienced chemists working in reputable laboratories The quantities of lead, which have significance in the examination of biological materials, are so small that only the most meticulous analytical work can be depended upon to provide the necessary data For both blood and urine either the dithazone or Fairhall methods may be used These are the methods of choice for urine For blood the spectrographic method has the advantage of requiring smaller blood specimens[30, 31, 3, 33, 34, 3]

Since urinary excretion of lead varies from specimen to specimen and from day to day, repeated specimens each at least 1 000 c c, are required for chemical analysis Spot samples can be utilized effectively by an experienced plant physician only in connection with the industrial control of lead poisoning in a plant They are quite inadequate for the diagnosis of lead poisoning in a particular case

Experience has shown that there is no consistent quantitative relationship between the amount of lead excreted in the urine at a particular time by a given patient and the existence of lead poisoning Cases of acute lead colic have been known to excrete very little lead in the urine On the other hand many workers who excrete lead in amounts far

above what is considered normal may show no evidences whatever of lead intoxication They are cases of lead absorption only

Since quantitative data are essential for the diagnosis of lead poisoning lead determinations in blood and urine and hematological studies of the blood should be carried out at the earliest possible moment As lead excretion continues and lead is stored in the bones it is gradually removed from the circulating blood Less lead then will be found in the blood or in the urine and since there is no method available for measuring stored lead in the body the laboratory findings at this later date will contribute little to a quantitative evaluation of the situation as it was when the patient s illness began

It is highly important for purposes of diagnosis to look upon lead poisoning not as a hard and fast clinical entity but rather as a subtle problem in toxicology where physiological and biochemical balances are shifting constantly a continuum as it were It is here that laboratory data if properly interpreted can greatly illuminate what is currently taking place in the body during the period the patient is under medical observation Repeated laboratory examination of blood and urine for their lead content and repeated hematological studies of the patient over an extended period of time will provide invaluable data as to current alterations in the inter relationships between lead absorption storage and excretion in the delicate balance between lead absorption as such and true lead poisoning

Laboratory data however also have their limitations As a reaction to prelaboratory days when a diagnosis of lead poisoning was made solely on the clinical picture there is a growing tendency to make a diagnosis on the basis of laboratory findings alone largely disregarding the clinical picture or seriously discounting it when laboratory findings are negative It should not be necessary to stress the importance of the clinical picture in every differential diagnosis Medical literature is full of warnings to physicians not to forget the patient while poring over laboratory reports concerning him and more and more there is a yearning for the old clinicians who because they had no laboratories to depend on became such keen observers and interpreted so intelligently the clinical pictures presented by their patients It is well to remember at all times that the *laboratory was never meant to be a substitute for good clinical* medicine

By far the most puzzling situations from the standpoint of diagnosis arise when laboratory reports one after another show occasional stippled cells with or without a very slight increase in the urinary lead

excretion This situation almost invariably leads to the practice of repeating the laboratory tests periodically, almost ad infinitum in the vain hope that perhaps a definite laboratory report one way or the other, will be obtained ultimately and the diagnosis then made in accordance therewith Actually in these cases conclusive laboratory tests are not often obtained, the patient becomes the despair of everyone and the result is that no proper investigation is ever made to determine what is really the matter with him What he needs is a completely fresh and objective re-evaluation of his condition by a good clinician

It is very rare in medicine to find a patient who presents a classical picture of any disease Good diagnosis is necessarily a synthesis on the part of the examining physician of many findings all interpreted in the light of his experience It is dependent not alone upon his knowledge and experience with the particular disease in question but upon his knowledge of the whole gamut of diseases because every diagnosis is in the last analysis a differential diagnosis There is great need at the present time for the application of good clinical medicine to the diagnosis of lead poisoning

Workmen's Compensation for Lead Poisoning

Before discussing some of the compensation problems in diagnosis which arise specifically in cases of lead poisoning, it might be well to consider briefly a few such problems which are common to practically all of the occupational diseases including lead poisoning

Most important perhaps is the need to prove the diagnosis in court frequently to a lay referee For as a practical matter, workmen's compensation is available not to a person who is suffering from an occupational disease but to a person who can prove that he has it It is the physician's task therefore, to prove it and this is disturbing He is not in the habit of approaching diagnosis with this in mind In his regular practice he makes a diagnosis solely for his own use in the treatment of his patient If at any time in the course of such treatment he has reason to reconsider its correctness he is at perfect liberty to do so in the light of his patient's response to therapy or any other experience which has developed in the case

In dealing with occupational diseases however, or suspected occupational diseases the fact that his diagnosis will be the subject of legal adjudication tends to make the physician uneasy, and he looks for short

cuts to diagnosis an approach which is quite foreign to his normal thinking In discussing lead poisoning in medical meetings for example physicians constantly ask for a few specific criteria upon which to make the diagnosis They are particularly partial to laboratory data which carry with them something of the magic of numbers Needless to say such short cuts are not to be found in medicine whether one is dealing with the occupational diseases or diseases which are non occupational in origin

Standardization of Terminology —For compensation purposes standardization of terminology is of great practical importance There are physicians who will not make a diagnosis of lead poisoning unless the patient is acutely ill Others take the position that the presence of stippled cells in the blood is in itself sufficient for such a diagnosis Still others use the term lead absorption for cases of lead poisoning in which the symptoms are relatively mild This loose use of terms without accepted definition adds seriously to the inherent difficulties in the medico legal interpretation of cases Common agreement however arbitrary with reference to the basic terms lead poisoning and lead absorption would be of inestimable value where litigation is involved

Lead Absorption —Lead absorption means nothing more than the absorption of lead into the body It implies nothing as regards toxicity Such absorption may be great enough to cause symptoms of disease in which event one would be dealing with a case of true lead poisoning On the other hand only a relatively small amount of lead may be absorbed i e too little to disturb the worker s sense of well being Within this group there may be a number of sub groups all cases of lead absorption In this general category one finds situations such as the following

1) Examination of a worker who considers that he is perfectly well may elicit clinical and/or laboratory evidences of lead absorption On careful questioning the worker might admit that he had noticed he was becoming more constipated than formerly that he has a peculiar metallic taste in his mouth at times that his appetite is not perhaps, what it used to be and so forth These things do not appear to be bothering him any Once they are called to his attention however he recognizes that they do exist in his case On physical examination one may or may not observe a lead line in such a worker However one usually observes a characteristic pallor of which the patient probably is unaware Laboratory examination of his blood and urine may disclose a few stippled cells and possibly a somewhat increased lead excretion in

the urine Such a case is still a case of lead absorption rather than lead poisoning and should be so classified

2) On careful questioning of such a worker one may elicit some of the symptoms previously indicated but find nothing on physical examination Nevertheless, there may be laboratory evidences of lead absorption

3) Physical examination may reveal a lead line or pallor without symptoms of any kind and there may or may not be laboratory evidences of lead absorption

4) The clinical history may reveal no symptoms whatever of lead absorption, the clinical examination also may be entirely negative and yet there may be evidences of lead absorption in the blood and urine

Lead Poisoning — When lead absorption is sufficiently great to disturb the individual's sense of well-being, i e when lead absorption reaches the stage of toxicity it results in true lead poisoning Such a worker does not have to have the characteristic symptoms brought to his attention by careful history-taking He comes to the physician with specific complaints because he does not feel well He seeks medical aid of his own accord This does not necessarily imply that he is suffering from acute lead colic or any other acute manifestation of the disease He may merely be suffering from troublesome prodromal symptoms which interfere with his sense of well being and for which he seeks relief In either event he is medically speaking a case of lead poisoning Lead poisoning is the toxic stage of lead absorption

Contraction of Lead Poisoning — The importance of a clear cut differentiation between lead poisoning and lead absorption and the practical need for standardization of the meanings of these terms comes up very pointedly whenever the question is raised as to precisely when a worker contracted lead poisoning This question arises wherever there are time limitation provisions in compensation laws

The following actual case illustrates very well the medico legal problems involved and the confusion of thought resulting from a lack of agreement as to the precise definitions of the terms used

A man who had been employed in one or another paint factory for approximately ten years without having lost any time from work because of illness suddenly developed acute abdominal pain for which he had to go home His doctor made a clinical diagnosis of lead poisoning and this was confirmed later by appropriate laboratory tests A claim for compensation was filed The diagnosis of lead poisoning was not challenged by the insurance carrier for the employer, but the claim

for compensation nevertheless was controverted on the ground that the man had contracted the disease a number of years before and could not therefore receive compensation the disease not having been contracted within the statutory period In support of this contending evidence was presented to the effect that during the three or four years previous to the acute attack, the claimant had been treated by his family physician for chronic constipation and minor gastrointestinal upsets which the latter had attributed to his occupation

On further examination however the doctor who had treated the claimant testified that he had regarded the case all along as one of lead absorption rather than lead poisoning because his patient was able to work and continued to do so that in his opinion the man contracted lead poisoning when he became disabled because of lead colic in the present illness Additional medical testimony on the question of precisely when the claimant actually contracted lead poisoning was conflicting and somewhat vague

On analysis however the various opinions presented may be briefly summarized as follows (a) that the claimant had contracted lead poisoning only when he became disabled from work thereby because of acute lead colic all that preceded having been due to various degrees of lead absorption though he may or may not have been aware of it (b) that he contracted lead poisoning when his gastrointestinal symptoms became sufficiently troublesome for him to consider it necessary to consult his family physician therefor and to receive treatment and (c) that he might have contracted lead poisoning at any time after he began working with lead ten years before that from the history no specific date could be fixed upon but that the evidence in the case clearly indicated that the disease had probably been contracted several years before

It was thus argued by the carrier that the claimant had very obviously been suffering from lead poisoning for a number of years and that his case was not therefore covered under the time limitation provisions of the compensation law Argument for the claimant on the other hand was to the effect that all that had preceded the attack of lead colic was undoubtedly due to continued lead absorption but that lead poisoning was contracted only when the claimant finally became disabled because of the attack of lead colic that he filed his claim immediately thereafter, and that he was therefore entitled to compensation

Many such instances could be cited where disagreement as to the meanings of the terms used resulted in protracted discussions which were very time consuming and irrelevant to the main points at issue

A failure to use terms only of accepted definition inevitably results in loose thinking and wastes the time of everyone. More than that, it may result in a gross injustice being done a worker, merely because of a general misunderstanding between the parties concerned.

Certain jurisdictions at the present time take legal cognizance of the distinction between lead absorption and lead poisoning. There it is recognized that a worker may absorb lead for a long time, that he may even show a lead line, have constipation or a poor appetite, and that evidences of lead absorption may be found in his blood and urine during the whole or any part of this period. Nevertheless, if he feels well and goes about his work unaware that there is anything amiss, he is considered to be a case of lead absorption. He does not legally contract lead poisoning until, as a result of disturbing symptoms, he begins to lose his sense of well-being, decides that there is something the matter with his health and considers it necessary to consult a physician, at which time the case automatically becomes a matter of record.

The practicing physician, who sees cases of lead poisoning, should be thoroughly conversant with the workmen's compensation laws of the jurisdiction where he is practicing. These laws differ from country to country, and in the United States of America they differ from state to state. He should have on his library shelves for ready reference at all times, the compensation laws governing his patients, so that he may protect adequately their rights under them. This is a civic as well as a medical responsibility. Unfortunately the practicing physician has not been trained to give these matters sufficient consideration in his practice. Plant physicians are necessarily far more aware of their responsibilities in this field.

Prevention

A growing sense of civic responsibility on the part of the public and of public agencies is fast becoming crystallized into a variety of legal concepts and requirements, the objective of which is Prevention. These include labor laws to provide safe and healthful working conditions, compensation for the injured with legal requirements for the reporting of these cases to the responsible official agencies and efforts to develop reporting for purposes of accurate morbidity and mortality statistics. Hence, the physician who acquires a patient, who says that he works with lead, finds himself in a somewhat unfamiliar environment,

one which involves many considerations and responsibilities beyond the purely medical problems as he knows them that of making a correct diagnosis for the purpose of treating his patient However the need to make a correct diagnosis in a case of lead poisoning has implications which go beyond the treatment of an individual patient or the prevention of lead poisoning in a given plant

Progress in public health and more particularly in industrial health is closely tied up with accurate morbidity and mortality statistics Such statistics provide basic data for the development of programs for prevention by appropriate agencies governmental and voluntary No accurate statistics in the field of lead poisoning will be possible until physicians recognize these cases and make a correct diagnosis, until they report them to appropriate State or Federal agencies as required by law Failure to report occupational diseases is common but this is due more often to failure to recognize the disease as occupational than it is to unwillingness to cooperate The end result however as a practical matter is a striking absence of accurate statistical data with reference to the incidence of all of the occupational diseases including lead poisoning This constitutes a major hurdle in the development of programs for prevention by public health agencies

At the present time failure to recognize a disease as occupational not only deprives the patient of his legal rights under the workmen s compensation laws but it may seriously jeopardize the patient s life For in cases where a particular chemical is responsible for the disease prompt removal from further exposure obviously is the first essential

Medical Control of Lead Poisoning in Industry

The prevention of lead poisoning in industry is not entirely or even fundamentally a medical problem It is inseparable from engineering control of hazardous lead processes and operations proper housing for the lead industries proper design of machinery so that lead may be processed with a high degree of safety suitable and adequate ventilation where indicated and meticulous housekeeping Periodic chemical air analyses are essential in order that exposure to lead may not exceed the 1 5 milligrams per ten cubic meters of air which is the accepted maximum permissible concentration

The plant physician can make important contributions in this field 1) He can by proper pre placement examinations make a sound selec

tion of personnel for the lead operations in the plant, 2) By intelligent medical supervision of the workers he can throw light upon particular processes or operations which appear to be responsible for excessive lead absorption or lead poisoning, 3) He can prevent individual cases of lead poisoning by proper medical surveillance of workers exposed to lead, 4) He can develop new toxicological data and so contribute to a better understanding of the medical problems underlying diagnosis and prevention Lead poisoning has been studied for generations, and yet many of the medical problems in this field still remain unsolved

Detection of Sources of Lead Poisoning in the Plant — In order to accomplish these objectives, the plant physician must work in close cooperation with management at all times through its engineering chemical and safety personnel He should receive regular reports of plant inspections of any air analyses which have been made of any control measures contemplated or introduced He in turn, must keep good medical records and be prepared to provide management with his current medical experience to supplement chemical and engineering data as to lead processes or working areas in the plant where exposure is too high and control measures are required

As a means of further supplementing chemical and engineering data as to lead exposure for purposes of prevention, an interesting medical procedure has come into use This involves the collection of group samples of urine from workers in specific locations for the purpose of having quantitative chemical determinations made of the lead content of the group samples [6, 7] If the number of workers included in the group is large enough this method may be very useful, having the advantage of providing cumulative data as it were with reference to recent overall exposure to lead in terms of absorption rather than the fragmentary data developed from periodic chemical analysis of air samples If such group urine samples are collected and analyzed properly if lead contamination is avoided and if the results are interpreted by persons experienced in this technique valuable data may be obtained as a basis for engineering control Its limitations are those of any statistical sampling method

In all biostatistical methods employed for the analysis of group data considerable caution must be observed because the group necessarily becomes more important than the individual and many variables tend to cancel out Complex clinical differences between workers including important differences in individual susceptibility to lead tend to become overshadowed in statistical tabulations The larger the series the less does

each worker's current medical status register since variations from the normal tend to be numerically small Nevertheless these differences between workers are of major importance in the prevention of individual cases of lead poisoning In handling group material for purposes of control therefore the plant physician should never lose sight of the worker as an individual

Furthermore in collecting and evaluating group medical data for purposes of control the plant physician should not confine his attention solely to evidences of lead absorption and intoxication Labor turnover the incidence of absenteeism the incidence of various illnesses not always directly traceable to lead may all throw light upon the need for better controls It is well known that workers who do not feel well often drop out of a plant before the precise cause has been determined

Personal Hygiene and Protective Equipment —This is a joint effort between management which must supply the protective equipment and the worker who must use it for his personal protection Here the plant physician can play a major role

Included in this general category are the following[62] 1) adequate facilities for washing including shower baths whenever possible 2) uniforms provided by management and regularly laundered 3) a separate lunch room free from lead contamination and readily accessible to washing facilities where provision is made for storage of lunch boxes brought from home and where whenever possible a nutritious hot mid day meal will be served including milk 4) two lockers for each workman one for street and the other for work clothes 5) respirators when required for special jobs of an approved type for the particular operation in question regularly tested properly maintained stored and distributed each day under proper supervision 6) educational literature and posters designed to get complete cooperation of workers in the lead control program These can be supplemented by safety talks either by the safety engineer the plant physician or the plant nurse

Group Surveillance of Lead Workers —Engineering controls and protective equipment however effective do not provide against personal carelessness on the part of individual workers or lack of proper understanding of the importance of protective measures for which they alone are responsible in the course of their work Close medical surveillance of lead workers therefore combined with a program of industrial health education in order to promote worker understanding and obtain individual cooperation, is one of the cornerstones in any prevention program

A program of periodical physical examinations of lead workers is the first essential. The frequency with which these examinations are to be conducted will be determined very largely by the extent and the nature of the lead hazard, the number of workers to be examined and the time the plant physician has available for this work. Thorough physical examinations of all workers at frequent intervals may be necessary at the start until a base line of experience has been developed. Thereafter, so called screening examinations of all workers every three to six months should provide necessary protection under ordinary circumstances.

Periodical physical examinations of large numbers of workers is an extremely time-consuming process, particularly because detailed records must be maintained. Moreover, the time available for such examinations is limited by the fact that the physician must spend a certain amount of time in the plant, so that he may be familiar with current plant processes and current plant problems. He must be available for conferences with plant engineers in matters of control. It is essential, therefore, that he adopt some routine procedure which will screen out with a minimum of effort those workers, who are obviously in good health, and permit him to give extra time to the others. The importance of such an approach is obvious when one considers the extent of the laboratory data required for a diagnosis in a single case of lead poisoning or the proper interpretation of lead absorption in a single individual.

Screening examinations can be brief and, nevertheless, include as a minimum an inspection of the worker for pallor, tremor and a lead line and a brief inquiry as to complaints referable particularly to the gastrointestinal tract and the nervous system. The weight, blood pressure and pulse rate should be recorded and samples of blood and urine taken with due precautions to prevent contamination. In addition to a blood count and hemoglobin determination one or more blood smears should be examined not only for stippled cells but for any evidences of a blood dyscrasia. The plant nurse can be of considerable assistance in following subjective complaints and observing such signs as pallor or tremor, when she sees workers in between periodic physical examinations, as when a worker comes to the medical office for a minor injury, for example, and promptly reporting any such abnormalities to the plant physician for his special attention.

Of great assistance in connection with screening examinations of workers is a rapid method for chemical analysis of lead in the urine which has been developed recently.[37] This makes possible the rapid

elimination by simple chemical methods of urines which contain only negligible amounts of lead. The others then can be analyzed further by the conventional more time consuming chemical techniques. By this process of elimination individual workers can be singled out for more comprehensive medical study.

Urine samples for lead cannot be collected in the plant without contamination unless there is a room completely free from lead dust which workers can enter only after showering. Similarly no attempt should be made to set up a laboratory for the analysis of these samples in a plant where contamination with lead dust is a possibility. In the absence of suitable facilities for collecting urine samples in the plant under supervision the worker may be given a lead free jug sealed in a bag to take home. At this time he should be given detailed instructions as to how to avoid contamination. While spot samples are not as accurate as liter samples, they may be very useful if carefully collected and interpreted with caution.

Testing for urinary porphyrines as a screening procedure for the selection of workers requiring special medical study is routine in some European countries. This method is being experimented with now in some of the lead plants in the United States. The results appear to be useful on the whole but there are still many problems which remain to be solved[70, 71]. It is a good addition to the screening examination but cannot as yet be regarded as a substitute.

All workers found to have significant abnormalities on the basis of the screening examination must be given a thoroughgoing physical examination including additional blood and urine studies. The purpose is not only to determine whether or not the worker is suffering from lead absorption or lead poisoning but to determine its extent and to formulate a program for the future management of the case.

There is much that is still to be learned with reference to the relation of diet to the prevention of lead poisoning. Nevertheless there is fairly general agreement to the effect that an adequate well balanced diet, including plenty of milk is of great value in that it tends to maintain the worker in optimum health. Milk is not only an excellent food but it is a convenient method of insuring an adequate intake of calcium and phosphorus. Since adults in general tend to suffer from a low calcium phosphorus intake ordinarily one need not be concerned about overdosage when giving milk[73]. Similarly vitamin D in the small amounts found in milk will be an aid to lead storage. While large amounts of calcium phosphorus and particularly vitamin D favor lead mobilization

rather than storage [8, 59, 60, 61], overdosage is more apt to occur when these substances are administered in pharmaceutical preparations than as generous amounts of milk in the diet

Protection of the Individual Worker — In his medical studies of individual lead workers the plant physician is in a particularly advantageous position He has an intimate knowledge of their lead exposure and he can control directly their future lead exposures in the plant Moreover in evaluating the physiological and biochemical responses to lead of the workers under his supervision the plant physician has the benefit of data obtained in pre-employment examinations which provide him with a base line for comparison Periodic physical examinations provide him with supplementary and comparative data, as exposure progresses, which are invaluable in enabling him to detect preclinical evidences of excessive lead absorption for purposes of prevention

These periodic physical examinations also are important in indicating trends such as increasing pallor increasing constipation, an increasing number of stippled cells, increasing amounts of urinary porphyrins and so forth Some plant physicians find that once a base line of trends for an individual worker has been established blood smears examined at frequent intervals for stippling alone can be used very effectively to prevent lead poisoning The plant physician who has sufficient background medical information with reference to each worker, is in a greatly favored position in this respect

Effectively to prevent lead poisoning among the workers under his supervision the plant physician must be a good clinician above all else It is on the basis of his clinical judgment that the lead workers in his plant are selected in the first place The decision will be his as to whether and when, a lead worker may return to his job after an illness whether or not the absence was due to lead poisoning Rotation of workers or the temporary elimination from further exposure to lead of a given worker must be decided on the basis of his physical findings and laboratory tests Each decision involves good clinical judgment, an intimate knowledge of the toxicology of lead, good differential diagnosis

The Small Plant — In the small plant the field of usefulness of the plant physician is far more circumscribed He is there on a part time basis, he may or may not have a part time industrial nurse to assist him there are no engineers or chemists available to make the necessary periodic technical investigations no air tests are made In general the plant physician is on his own to do what he can with very limited funds

available for laboratory work in connection with clinical examinations He is apt to be underpaid and not paid at all for time spent outside his medical office getting acquainted with plant operations

It is well therefore to remind him that he can turn to the Divisions of Industrial Hygiene in governmental agencies for medical chemical and engineering assistance without charge on a consultation basis When several small plants can be persuaded to pool their medical services greater effectiveness is possible This seldom is comparable however to the facilities a plant physician has available to him in a large, well organized plant where management is working in close cooperation with him

In the small plant therefore what the plant physician will accomplish is largely dependent upon his clinical acumen his knowledge of lead poisoning and equally important his personality energy initiative and imagination

The Practicing Physician and Prevention

It is not only the plant physician who is in a position to prevent lead poisoning although his contributions are necessarily of primary importance The practicing physician in his office also can play an important role in prevention particularly if he is practicing in the neighborhood of a lead plant but wherever his office he will see patients who are working with lead at the time they come to consult him or who have had significant lead exposures in the past

The occupational history the clinical picture of lead poisoning and the laboratory evidences of lead absorption which have been discussed in some detail will all help him to detect early cases of lead absorption or lead poisoning in his practice and by being alert to the interrelationships between absorption storage and excretion he will be in a position to assist intelligently his patient in maintaining a balance favorable to health In so doing he will be making a positive contribution to the prevention of lead poisoning

A correct diagnosis by the practicing physician however whether of lead absorption or lead poisoning is important not only to his patients but to public health agencies whose programs for prevention are necessarily based upon correct estimates of the incidence and distribution of the disease The practicing physician can make a major contribution therefore to the prevention of lead poisoning over a broad front by

1) being sure his diagnosis is correct and 2) by reporting his cases promptly to the properly constituted public health authorities.

Treatment

When prevention fails, proper and prompt therapy becomes a matter of great urgency. Relief of acute lead colic is perhaps the simplest aspect of the problem; it is effective and dramatic.[3] Therapy in acute encephalopathy is more difficult, less specific and usually less effective. Neuritis or paralysis, whether they result from prolonged exposure to lead in the absence of an attack of acute lead poisoning or develop as sequelae of such an attack, are to be treated very much the way similar pathological conditions are treated when due to other causes. Immediate removal from further exposure to lead is imperative in all cases. Prompt hospitalization is highly desirable.

Underlying all treatment is the need to establish and maintain a physiological and biochemical balance between storage and excretion which is favorable to health. Lead absorption presumably has ceased with the removal of the patient from his work, once his bowels have been evacuated of their fecal lead contents. The effectiveness of therapy largely depends upon the physician's understanding of the dynamics of this disease, of the mechanisms at work in its production and of the current changes in the balance between storage and excretion which occur in the course of treatment. It depends upon his ability to manipulate by therapy these balances to the advantage of his patient and to maintain a favorable balance during convalescence and until complete recovery has been effected. More than anything else this requires a vast amount of experience and the good medical judgment which develops with experience. There can be no hard and fast rules, but a few words of general guidance may be useful.

Acute Lead Colic

Prompt administration intravenously of 10 ml. of a 20 per cent calcium gluconate solution produces dramatic relief of symptoms. The patient will stop writhing with pain and may go to sleep. This often settles any questions still pending as to whether or not one is dealing with one of the acute surgical conditions of the abdomen which symptomatically resemble lead colic.

This dose may be repeated intramuscularly if pain recurs or continues after the patient awakes Under this regime an uncomplicated case of acute lead colic usually will subside completely Other drugs which relieve spasm of smooth muscle such as atropine in large doses or nitroglycerine may be used as adjuncts to the calcium gluconate Calcium chloride may be used instead of calcium gluconate (5 ml of a 10 per cent solution) but it can be administered only intravenously Morphine or other sedatives should never be given as long as any doubt remains as to whether the condition is surgical or not

Once surgical conditions of the abdomen have been definitely ruled out it is permissible to give morphine if required Early evacuation of the bowels by cathartic or enema becomes imperative primarily to remove fecal lead and prevent further lead absorption Plenty of fluids to promote lead excretion by the kidneys also is indicated Magnesium sulphate is favored as a cathartic in these cases

Milk usually is well tolerated when acute symptoms have subsided, and its calcium phosphate and vitamin D content may be useful in promoting lead storage Overdosage with calcium phosphate and vitamin D particularly possible in drug therapy should be carefully guarded against since this tends to promote mobilization rather than storage Similarly the use of potassium iodide which tends to mobilize stored lead is contraindicated at this time Injections of calcium gluconate are no longer useful after the acute attack has subsided and should be discontinued The liver should be supported for a long time by diet and other measures

Acute Lead Encephalopathy

Prompt relief of manic symptoms convulsions and nervous excitability is the problem here This can be accomplished by sedatives preferably the barbiturates Hypertonic salt solution intravenous glucose and the usual supportive measures which are employed to meet a condition where a patient is suffering from dehydration cerebral edema tissue starvation and exhaustion are in order[9]

Neuritis and Paralysis

Whether or not these conditions have developed gradually over the years or follow an acute attack of lead poisoning as sequelae the problem

falls into three main categories 1) prompt removal from exposure to lead 2) therapy directed toward removal of lead from the circulating blood and 3) the usual measures for promoting the nutrition and the repair of nerve tissue the prevention of contractures and deformities the promotion of better muscle tone, etc Physiotherapy expertly applied in conjunction with proper management of the underlying lead intoxication will be of great value in these cases

Deleading Therapy

Deleading therapy has as its objective the removal from the body of readily mobilizable lead with a view to preventing a subsequent attack of acute lead poisoning due to such mobilization This procedure is most effective in cases where lead storage has been relatively recent Old deposits are so situated in the bones as not to be readily mobilized by this technique[10]

Deleading therapy combines low calcium intake with the establishment of an acidosis in the patient It is a delicate procedure requiring hospitalization of the patient and considerable experience not only with lead poisoning but with the acidosis therapy as used in other medical conditions Total lead excretion is to be measured

A low calcium diet involves the complete exclusion from the diet of milk in any form, of eggs and of green vegetables After the low calcium regime has been well established ammonium chloride is given for about a week, starting with one gram three times daily before meals preferably in enteric coated capsules This dose is gradually increased to six or eight grams per days The usual symptoms of acidosis develop with loss of appetite loss of weight and sometimes nausea and headache The whole procedure should progress very slowly and very cautiously Too rapid mobilization of lead may precipitate an acute attack of lead poisoning Too severe an acidosis is dangerous Patients tend to react very differently to this therapy, and the closest possible medical supervision is essential

There is serious difference of opinion among experts as to the desirability of deleading procedures under any circumstances It should be attempted only by a physician with considerable experience in this technique

Convalescence

The duration of convalescence and the completeness of recovery depend upon many factors most important of which are the interest experience and intelligence of the physician in charge of the case Detailed knowledge of the biochemistry of lead in the body is of great importance[6] Beyond that the course is influenced by the severity and duration of the illness the existence of other clinical disease entities whether or not they were aggravated by the lead poisoning the opportunity given the patient to combine relaxation and rest with a program of rehabilitation so that neuroses have no chance to develop and the patient s native ability to re establish normal physiological function once it has been disturbed for any reason A good general hygienic regime under supervision is required This includes plenty of fresh air good nutritious food plenty of milk and freedom from psychological stresses and strains

Working during convalescence is in general undesirable unless fatigue can be avoided Particularly night work or changing from one shift to another which requires adaptation to changes in meal schedules is not well tolerated Meals for a patient recovering from lead poisoning should follow as regular a routine as possible This helps very much in re establishing normal functioning of the gastrointestinal tract Control of constipation and plenty of fluids continue to be essential during this period

A worker who has recovered from an acute attack of lead poisoning should never again work with lead He may return to his previous work only if the possibility of further exposure there has been eliminated In a very special case the use of an air line respirator may make it possible for him to do his regular work under medical supervision Such a step should however be taken with great caution In any event every patient should be kept under close medical supervision during the first few weeks after he resumes work and more casually for a while thereafter

BAL

This substance known as British Anti Lewisite (3 dimercapto propanol) was developed by the British during World War II as an antidote to arsenic in war gases It has since proved effective in the treatment of industrial arsenic poisoning and acute mercury poisoning

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Experimental treatment in lead poisoning has thus far proved ineffective. However, variations in the formula are under investigation, and a related drug very possibly may be available for the treatment of lead poisoning in the not-too-distant future[66, 67]

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XV

MAGNESIUM

By IRVING R TABERSHAW

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INDUSTRIAL USES

Magnesium is a silvery white metal of extreme lightness being one third lighter than aluminum and one fourth of the weight of iron but of great structural strength It can be cast wrought welded riveted formed and machined and is finding increasing use wherever strength lightness and motion are important for example in airplanes portable tools household appliances machinery etc The production of the metal has increased enormously since the method of extracting it from seawater by an electrolytic technique was perfected The salts and alloys of magnesium are also used widely in medicine The most common form in which industrial users come in contact with the metal is as magnesium alloys which are sold under various trade names

HAZARDS FROM USE

The health hazard through the use of magnesium is secondary to the fire hazard incident to machining or grinding magnesium alloys In the molten or finely divided state the dust is easily ignited and burns

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taminated with magnesium dust with implantation of minute particles of magnesium or its alloys There is a rapid accumulation of gas beneath the skin and the lesion may simulate a rapidly developing gas gangrene There is no laceration or damage to muscle tissue and the gas spreads subcutaneously and along the tissue planes The tumor mass and crepitation spread rapidly from the point of injury The patient is relatively asymptomatic with no fever unless secondary infection supervenes The white cell count rises but is not excessive Cultures of the lesion show no growth either aerobic or anaerobic The temperature pulse and respiration remain only slightly elevated and the patient has no toxic symptoms

Differential diagnosis is chiefly between a gas gangrene infection and the syndrome of hemolytic streptococcic gangrene

Treatment

The treatment of a penetrating wound produced by magnesium is expectant and surgery is not indicated Rest of the part usually the arm wet dressings and supportive therapy usually will result in cure in several days A culture for purposes of differential diagnosis is imperative and if no hemolytic streptococcic or gas bacilli are found the patient should be treated expectantly Secondary infection or concomitant infection should be treated by the use of antibiotics and surgically by incision and drainage

Prevention

In most industrial uses of magnesium the danger of fire limits the amount of atmospheric contamination with dust particles as safety engineers are extremely cognizant of the hazard The ordinary safety precautions should be taken against accidental contamination with magnesium alloys Splinters of magnesium metal should be immediately removed and wet dressings applied

from handling the molten metal are rather common The dust may be inhaled producing typical *metal fume fever* Inhalation of magnesium dust from industrial processes is not common, since the fire hazard makes it mandatory that atmospheric contamination with high concentrations of dust be controlled Magnesium will produce a dermatitis on the abraded skin The chief problem involved in its use, from a health standpoint is the introduction of minute particles under the skin through contaminated tools or splinters of the metal or its alloys In spite of extensive use no cases have been reported from the basic magnesium industries

In medicine the metal has been used as an absorbable suture in the internal fixation of fractures and in promoting drainage from the interior chamber of the eye These uses now have been largely abandoned

Pathology

Contact of magnesium and living tissue produces a chemical reaction due to the effect of magnesium on water producing magnesium hydroxide and free oxygen The liberation of magnesium hydroxide causes an alkaline necrosis of tissue whose extent depends on the dissolution rate of the metal The gas is trapped in locules producing gaseous tumors which are absorbed gradually Fibrotic proliferation occurs in attempting to repair the necrosis and if continued over a long period of time, a granulomatous lesion containing gas is formed This granuloma may produce pressure effects on adjacent tissue and organs After the gas is absorbed a dense scar is left

The rapidity of tissue destruction and repair is dependent on the surface area of the magnesium Rapid effects are noted with dust and powder and slower effects with splinters and wires made of the metal The tissue reactions are successively edema muscle degeneration and infiltration with lymphocytes and macrophages although some polymorphonuclear leukocytes are present Gas formation may become prominent within a few hours

Diagnosis

The diagnosis of a magnesiogenous granuloma depends on a history of contact with a penetrating object composed of this metal or con

XVI

MANGANESE

By RONALD F BUCHAN

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Manganese generally is used to produce a hard steel of great tensile strength Manganese is also used in alloys with arsenic tin boron zinc copper aluminum and bismuth Spiegeleisen silicospiegel ferromanganese and silicomanganese are the most important alloys The greatest source of occupational exposure is in the extraction of the manganese from the ore although those workers utilizing it in the manufacture of matches and fireworks deodorants germicides disinfectants glass pottery bleaching of textiles and in the manufacture of batteries and glazes are also subject to toxic exposure

CHRONIC INTOXICATION

Acute manganese poisoning has not been described The syndrome observed in manganese intoxication usually is due to prolonged exposure to manganese Characteristically the central nervous system is affected Patients with chronic manganese poisoning manifest propulsion and retropulsion which may be particularly evident on inclines In addition in varying degree and various cases will be noted scanning speech stuttering speech, micrographia pathological impulsive weeping and laughing lassitude easy fatigability and mask like facies Tremors fine and gross of trunk and limbs may be apparent as may be a retardation of movement and thought

Edsall and associates[1] in reviewing the data on manganese intoxication enumerated the following commonly occurring symptoms lassi

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cation Impairments of liver or kidney functions are not ordinarily observed

TABLE I

Impairment	Percentage Affected	Percentage Exposed Not Affected	Percentage Nonexposed	Numbers of cases Affected	Numbers of cases Exposed Not Affected	Numbers of cases Nonexposed
Total examined	100	100	100	11	23	16
Lassitude	91	4	0	10	1	0
Drowsiness	91	4	0	10	1	0
Gait disturbances	91	0	0	10	0	0
Dyspnoea slight	91	0	0	10	0	0
Tremor of body or extremities	91	0	0	10	0	0
Muscular weakness	82	4	0	9	1	0
Muscular cramps	8	9	[illegible]	9		1
Speech disturbances	73	0	0	8	0	0
Sexual disturbances	73	17	0	8	4	0
Metallic taste	64	0	19	7	0	3
Vertigo	55	4	6	6	1	1
Paraesthesia	55	0	6	6	0	1
Palpitation	55	0	6	6	0	1
Anorexia	45	4	6	5	1	1
Muscular pain	45	0	0	5	0	0
Twitching of fingers	45	0	0	5	[illegible]	0
Headache	45	35	19	5	8	3
Joint pains	[illegible]	4	0	4	1	0
Increased perspiration	36	0	6	4	0	1
Salivation	27	0	0	3	0	0
Impulsive weeping	27	0	0	3	0	0
Impulsive laughter	27	0	0	3	0	0
Difficulty in swallowing	18	0	0	2	0	0
Violent temper	18	0	0	2	0	
Nausea	18	0	0		0	0

Canavan and associates[5] describe the post mortem findings on a case dying from intercurrent cardio renal disease 14 years after the appearance of symptoms attributable to manganese Gliosis satellitosis and degeneration of the nerve cells of the basal ganglia were observed Atrophy of the cortex was evident as was atrophy of the striate bodies and optic thalami There was thickening of the choroid pia mater Casamajor[6] and Ashizawa cite the autopsy findings in 2 additional cases complicated however by extraneous pathology Casamajor reported degeneration of the longitudinal fibers of the pons and Ashizawa noted extensive changes in the caudate nucleus and putamen with a greater degree of degeneration in large ganglion cells as opposed to the smaller cells

tude fibrillations, fine and gross tremors of the limbs trunk and head, nocturnal cramps of the calves tendon reflex exaggeration, ankle clonus retropulsion and propulsion slapping gait, uncontrollable laughter and weeping It is emphasized that an occupational exposure of three or more months is ordinarily observed before onset of any symptoms Gastrointestinal genitourinary ophthalmological and sensory disturbances were not observed and laboratory data was non contributory

Several cases were described in the next few years and McNally reviewed 131 cases in a careful clinical appraisal He listed 81 signs symptoms and conditions observed by various authors He pointed out that many of these were duplications and the use of synonymous terms for the same or similar signs or symptoms He estimated the incidence of these various symptoms in the following manner peculiar gait, all cases weakness in legs and tremors 88 per cent mask-like face 83 per cent impulsive laughter 70 per cent, propulsion and retropulsion 70 per cent tremors of the whole body or extremities 70 per cent monotonous speech or disturbed speech 60 per cent fatigue 52 9 per cent increase of tendon reflexes 50 per cent all reflexes exaggerated 50 per cent sudden onset 50 per cent, spastic gait 46 per cent pains in the arms back and legs 36 per cent, impulsive weeping 26 per cent disturbances of sexual function 25 per cent all other symptoms less than 5 per cent The United States Public Health Service[3] in an extensive clinical appraisal indicated the incidence of neuro muscular symptoms as noted in Table I

Flinn Neal and Fulton[4] studying 34 exposed workers in an ore crushing plant found 11 suffering from manganese intoxication The clinical picture was similar to that related by Edsall and associates with the exception of leucopenia which was observed in the worst cases Pertinent engineering epidemiological data is included in their report

From the pattern of symptoms described it will be apparent that one must differentiate from degenerative diseases of the nervous system particularly progressive lenticular degeneration (Wilson's Disease) multiple sclerosis Parkinsonism and amyotrophic lateral sclerosis The occupational history will assume primary significance as there are no consistent laboratory data which will be helpful except for the leucopenia noted by Flinn and associates in their series Flinn and associates in their studies report also a decrease in neutrophils lowered blood calcium and a minimal reduction in the middle zone of Lange s test

Urinary excretion of manganese is as in the case of lead indicative of exposure and degree of exposure rather than as an evidence of intoxi

hygiene control of tremors and rigidity Preparations of the belladonna series and synthetics of similar action e g artane may be used according to indications Dosage must be regulated to achieve a balance between effective relief and disturbing side actions However little success has attended all attempts at therapeutic alleviation of manganism Positive efforts must be exerted in diet maintenance with attention to proper elimination and secondary anemia Efforts to readjust the lowered blood calcium if present will do no harm although no favorable response has been noted in such cases Johnstone[7] cites a possible contraindication to the therapeutic use of thiamine hydrochloride It has been observed experimentally that thiamine hydrochloride in large doses will encourage the retention of manganese McNally[13] relates his experience with sodium thiosulfate 1 gm in 10 c c aqueous solution intravenously on alternate days It was believed the patient showed some amelioration of symptoms Charles[14] used intravenous liver 15 to 30 units daily for 4 days with some improvement, most apparent in the initial period of treatment

Cases of short duration and exhibiting mild symptomatology may improve radically upon removal from the toxic atmosphere In such cases of course the patient should be removed from the toxic atmosphere and should not return to exposure Those patients with severe symptoms will show little or no permanent improvement at any time

Voss[8] on the other hand, reporting on an autopsy of a case of manganism dying from bronchopneumonia described changes in the right pyramidal tract and in both sciatic nerves but not in the basal ganglia Pneumonia or pneumonitis has been stated by several authors to be a common phenomenon of manganese exposed subjects Scandinavian[9] and European[10] reports have attributed increased community incidence of pneumonia to nearby manganese smelters Animal experiments have not confirmed the human observations Davies[11] considers that manganese has a specific toxic reaction on respiratory epithelium

Over the years there has been apparent some lack of agreement in regard to the period of exposure necessary to develop manganese intoxication with reports varying from one and a half months to twenty years However, as reports accumulate, it would seem that many workers who become affected, do so during the first 2 years of exposure The incidence of those affected in relation to the total number exposed to the same hazard seems to be variable This is probably due to fluctuations in degree and nature of exposure and variation of detail in epidemiological techniques

Prevention

Prevention is largely dependent upon proper engineering control making full use of local and general exhaust of ventilation wet drilling processes mechanical conveyors and mixers Air samples should be taken periodically to measure the effectiveness of mechanical control measures Strict medical control should be a concomitant procedure with examinations made at least every three months with particular inquiry into symptoms referable to the central nervous system and accurate evaluation of neurological signs or symptoms It should be remembered as with most industrial toxins the portal of entry is through the respiratory rather than the gastrointestinal tract and preventive measures should be directed towards the maintenance of dust free working atmosphere in accordance with the best tenets of modern industrial hygiene practice

Treatment

There is no specific therapy for manganese intoxication Management as in parkinsonism may be directed toward adequate mental

XXII

MERCURY

By RONALD F BUCHAN

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Mercury is used industrially as the pure element and as a number of its compounds mercury itself being used in switches vacuum pumps and retorts and in scientific laboratories Mercury cyanide is used in the manufacture of germicidal soaps in photography and in manufacturing cyanogen gas Mercury nitrate is utilized in the mercuric and mercurous forms mercuric salts being used as a carroting agent in the manufacture of felts in ointments in medicines and as a nitrating agent in making intermediate and organic chemicals Mercurous salts are used in the manufacture of mercury acetate in cosmetics in medicines, as a laboratory reagent and for blue blacking metals. Organic mercurial products such as ethylmercury phosphate chloride or hydroxmercuric compounds are utilized for treating seeds to kill fungi and prevent seed rotting or damping off They are also used as components of marine paints to prevent barnacle accumulation Numerous other uses are listed by Schwartz and associates[1]

OCCUPATIONAL POISONING

The usual industrial disease arises from prolonged and chronic exposure with resultant effects on the mucosa of the gastrointestinal tract particularly the mouth and deterioration of the nervous system Systemic absorption may occur through the respiratory and alimentary tracts In addition absorption through the skin is a common source of industrial intoxication Agate and Buckell report 7 cases of mercurialism in the fingerprint staff of the Lancashire Constabulary Gray powder metallic mercury triturated with two parts chalk has been used widely in Britain and the United States for eliciting latent finger

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as the upper limit of safe exposure Attainment of such a degree of mechanical control does not obviate the need for medical control

Alimentary and integumentary absorption may be controlled by instruction in hygienic habits and the use of clean and protective garments according to the nature of exposure

Following the basic preplacement examination exposed workers should be interviewed at least every months with particular attention to medical history and observation of buccal mucosa teeth and peripheral reflexes The examining physician should become so familiar with his patient that psychic changes as manifested in mood and disposition will be detected in the early stages In addition the worker may be asked to write his name Early tremors may be readily elicited in this manner Positive physical findings demand an immediate appraisal of mechanical and hygienic control measures Atkinson[4] has described a brown reflex obtained from the anterior capsule of the lens in workers absorbing mercury This would seem a useful and easily applied routine measure in the periodic examination of such workers Routine hemoglobin determinations and urinalyses are indicated at the time of each physical appraisal

BAL[5] (2 3 dimethylmercaptopropanol) has been useful in the treatment of acute mercurial poisoning 5 mgm /kg or 3 c c of a 10 per cent solution is administered intramuscularly at once followed by 2 5 mgm /kg in 2 hours Repeat 2 5 mgm /kg in four hours up to 3 additional doses depending upon the condition of the patient On the succeeding days up to the fourth day 5 mgm /kg may be administered once or twice during the 24 hour period according to the progress of the patient The foregoing regimen must be started immediately for results which may be anticipated as excellent With a delay of 2 hours or more the effectiveness rapidly disappears Shock must be treated in the usual manner with fluid plasma blood heat and stimulants according to the indications If the portal of entry has been gastrointestinal milk or raw eggs should be administered and evacuated by lavage Follow lavage with 5 per cent sodium formaldehyde sulfoxylate solution lavaging again but leaving approximately 250 c c of sulfoxylate solution in the stomach Concurrently BAL should be administered as already described

There has been little effective palliation of chronic mercurialism Benzedrine sulfate has been utilized 20 to 30 mgm twice daily usually in conjunction with an atropine derivative or substitute Further elucidation is necessary in regard to the role of BAL in chronic intoxication

prints The portals of entry in Agate and Buckell's cases probably were alimentary, respiratory and integumentary. Stomatitis and salivation have long been considered as typical symptoms of mercurialism although it is not as common in occupational finding as the older literature might lead us to believe. Turgescence, swelling and bleeding of the gums and ulceration may be noted. Involvement of the nervous system is one of the most common findings and is represented by tremors and nervous irritability which are aggravated by attention or intention. As an early sign its presence usually can be demonstrated by asking the workman to write his name. Observation while he is working may be sufficient to precipitate a manifestation of accentuated irritability. In addition to the tremors there are readily noted lack of confidence, lack of concentration, fear, restlessness, irritability and depressive state. This has been described by Kussmaul as *erethism*. The intention tremor may be widespread involving the fingers, tongue and eyelids, the fingers and eyelids being most commonly subject to this phenomenon.

Acute occupational poisoning will arise generally by accident or by suicidal intent. Williams and Schram[3] report such an instance involving 32 workmen. It is conceivable that volatilization of mercury or its compounds in massive amounts could be productive of acute mercury poisoning similar to that seen upon ingestion of mercury or its toxic compounds. Dermatoses are not uncommon as mercury compounds may be irritant or sensitizing to the skin. Mercuric nitrate, mercury fulminate, mercuric iodide and mercury bichromate have all caused skin irritation. The lesions are often in the nature of chemical burns although varying degrees of contact dermatitis will be observed.

In the chronic cases there are no particular diagnostic laboratory criteria although there usually is a concomitant secondary anemia and one may find occasional urinary blood cells or casts indicative of some renal damage although this is not usual in the chronic exposures. With acute intoxication one will find evidence of severe gastrointestinal and renal damage.

Prevention and Treatment

Prevention is dependent upon engineering control to remove the emanated fumes and dust of mercury and its compounds so that they may not be inhaled by workers utilizing such materials or by workers in the neighborhood of such processes. The American Standards Association has endorsed 1.0 mgm. of mercury per 10 cubic meters of air

XVIII

NICKEL

By RONALD F. BUCHAN

Nickel is widely used in industry and ordinarily encountered as nickel ammonium sulfate which is utilized in the manufacture of paints varnishes and ceramics for nickel plating blackening brass and zinc as a mordant in dyeing and printing textiles and as a catalyst for oils

Nickel is prepared also from nickel carbonyl which is a volatile substance and when inhaled has a destructive effect on the endothelium of the capillary vessels leading to hemorrhage in the brain adrenals and other organs With the circulatory weakness there is an attendant dyspnea cough expectoration tightness in the chest nausea pain in the forehead faintness and raised temperature Fortunately such exposures are not common but when they do occur can have fatal consequences the clinical picture being that of acute bronchitis or bronchopneumonia McNally[1] remarks on the cases of Katzing Brandes and Armit all of which follow substantially the same pattern Bayer also states that his experience reveals the acute respiratory reaction with headache dizziness cough marked dyspnea fever and leucocytosis In mild cases the patients were symptom free in 8 to 14 days Fatal cases revealed on autopsy equal hepatization of the lungs the alveoli being stuffed with fibrin and few cells The most common manifestation of industrial disability due to nickel is the so called *nickel itch* ordinarily a sensitivity dermatitis due to nickel sulfate rather than a contact dermatitis although the first manifestations may be quite localized with all the appearance of a local contact dermatitis Schwartz and associates[3] give a detailed epidemiological study of this reaction Hardening the development of resistance to the sensitizing seems to occur with some regularity in workers exposed to nickel sulfate Consequently one should not indiscriminately advise the permanent removal of workers from such contact

The question of respiratory tract neoplasm has been raised in regard to nickel British experience seemingly has indicated a higher than chance incidence of cancer of the nasal passages and lungs in nickel

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XIX

PHOSPHORUS

By ALICE HAMILTON

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Phosphorus, once the most dreaded and spectacular of the industrial poisons, is now almost negligible. The effects of phosphorus poisoning in match makers were so visible and so distressing to see that the sympathies of the public were enlisted readily in the efforts to combat it, and after all forms of governmental regulation had been tried and it had been proved that the only way to put a stop to phosphorus poisoning was to abolish the use of white phosphorus in the making of lucifer matches, the principal civilized countries adopted this very radical procedure and now the making and sale of white phosphorus matches is carried on only in the Orient[1]

White Phosphorus. Lucifer matches were made first in 1833, and the disease known as "phossy jaw" was reported first by Lorinser of Vienna in 1845. Soon after that, cases were discovered in practically all European countries and in the United States. The reason for the widespread attention given to this form of occupational disease is not its great prevalence, for only a minority of those exposed suffer: 70 among 600 workers in Silesia in [illegible]0 years, 70 among 620 in 21 years in France; nor because it is so deadly, the mortality is from 2 to 20 per cent; nor because it is rapid and violent in its manifestation, for it is slow to an unusual degree; but because it is extremely painful, it attacks the bones of the jaw and results in great deformity which is visible to everyone, and it is accompanied by a fetid discharge which makes the victim a misery to himself and others. The essential factor in phosphorus poisoning is the action of the fumes on the periosteum, almost always of the maxillae, to which they gain access after removal of a tooth. Necrosis sets in and then a suppurative process caused by sec

refinery workers This subject probably will receive increasing attention as is currently the case with chromium

Prevention of intoxication due to nickel is dependent again upon engineering control Fortunately, the processes, which are used to obtain pure nickel generally are well enclosed, the chemical reaction being conducted in a closed system (Mond process) obviating serious injury unless there is accidental leakage If such should occur the worker should be removed from exposure as quickly as possible The rescuers should utilize an air line respirator Oxygen should be administered, and on removal to hospital the patient should be placed in an oxygen tent or oxygen administered by mask or intranasally Glucose in 50 per cent concentration intravenously is helpful in reducing the pulmonary edema which may appear quickly or not until several hours after the incident Protective clothing, gloves and intervals of non exposure may make it possible for such patients to continue their occupation with decreasing and disappearing skin reaction to the sulfate

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White Phosphorus Lucifer matches were made first in 1833 and the disease known as phossy jaw was reported first by Lorinser of Vienna in 1845 Soon after that cases were discovered in practically all European countries and in the United States The reason for the widespread attention given to this form of occupational disease is not its great prevalence for only a minority of those exposed suffer 70 among 600 workers in Silesia in 20 years 70 among 6[illegible]0 in [illegible]1 years in France nor because it is so deadly the mortality is from [illegible] to 20 per cent nor because it is rapid and violent in its manifestation for it is slow to an unusual degree but because it is extremely painful it attacks the bones of the jaw and results in great deformity which is visible to everyone and it is accompanied by a fetid discharge which makes the victim a misery to himself and others The essential factor in phosphorus poisoning is the action of the fumes on the periosteum almost always of the maxillae to which they gain access after removal of a tooth Necrosis sets in and then a suppurative process caused by sec-

ondary infection through the pus organisms present in the mouth, then abscess formation fistulae and the cachexia of chronic septicemia Victims of "phossy jaw" in extreme cases die of this septic process, in slower cases they are likely to develop tuberculosis Exceptionally the periosteum of other bones is attacked and there may be fragilitas ossium

The match now made is the safety match, for which amorphous red phosphorus is used and the "strike anywhere" match made with the sesquisulfide of phosphorus neither of these having the poisonous properties of white phosphorus In a French match factory Nicolas and his colleagues found that there was a great deal of skin disease from the handling of phosphorus sesquisulfide It was a rapidly developing erythema with formation of vesicles or pustules and accompanied by severe subjective sensations and sometimes, by conjunctivitis Greasy skins were most susceptible They produced in volunteers an eruption with the paste and also with the powder A wash of potassium permanganate and sodium bicarbonate caused prompt recovery

Cases of phosphorus poisoning, however, are still reported from other industries chiefly the production of phosphorus the chemical industry the manufacture of phosphor bronze and making lights for miners lamps In Great Britain most of the cases of phosphorus necrosis coming to the knowledge of the Factory Inspection Department have occurred in the production of phosphorus

A sudden and unexpected reappearance of severe phosphorus necrosis took place in the United States in 1923–26 when a new kind of fireworks was manufactured in three factories on the Atlantic seaboard with the use of white phosphorus The management was ignorant and reckless and as a result 14 workers all but 1 being women had developed extensive necrosis of the jaw and 2 had died of septicemia The period of exposure was short only 6 months in 1 case So far as is known this kind of fireworks no longer is made (Ward[3]) The production of phosphorus and its compounds gave rise to 3 cases as described recently by Heimann[4] of the New York State Department of Labor The men were working with white phosphorus converting it into the red allotrope The precautions taken in the factory for the protection of the men included routine medical and dental examination the latter with x rays yet in spite of this the 3 men developed phosphorus necrosis of the jaw after exposures of 2, 8 and 13 years respectively The one who had the shortest exposure recovered with no deformity the one with exposure of 8 years was left with a loss of all the teeth of the lower jaw and part of the lower jaw bone with some facial deformity, the

third man had involvement of both upper and lower jaws lost a large part of the palate bone and there were fistulous tracts from mouth to nose and to the nasal sinuses The condition 18 months later was still active Yet a dental examination made only a month before had shown a normal picture

The Tennessee Valley Authority is faced with a possible hazard in connection with a new method of producing white phosphorus by an electro-thermal process The phosphorus is to be used for the production of phosphate fertilizer

Phosphoretted Hydrogen Phosphine PH_3 sometimes is encountered in the production of acetylene and also in the use of an acetylene torch supplied with impure gas It is found also in the decomposition of ferrosilicon under the influence of moisture (Zernil) It is excessively toxic resembling arsine in its action except that it is not hemolytic (Baader[6]) Carlisle in an article on pulmonary edema in war plants mentions among the noxious agents which may cause such a condition phosphorus oxychloride trichloride and pentachloride

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SELENIUM

By RONALD F BUCHAN

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Selenium has many industrial uses Table I illustrates the more common uses[1] Workers utilizing selenium in the processes indicated are subject to exposure to selenium its oxides hydrides and organic vapors Workers in the vicinity of such operations also may be exposed to noxious concentrations

TABLE I

Glass decolorizer	Alloying of free machining copper base alloys
Production of ruby glass	Rubber accelerators and anti oxidants
Red and yellow glazes	Fireproofing of electric cable
Paint and ink pigments	Photoelectric apparatus
Production and coloring of plastics	Chemicals
Alloying of machinable stainless steels	

Acute and chronic selenium intoxication is well recognized within industry, although there is a relative paucity of reported cases The degree of exposure may be very slight and with hydrogen selenide exposure to less than one tenth part per million (0 1 p p m) will be productive of disabling gastrointestinal and respiratory effects

Acute Intoxication

Acute intoxication which may arise from exposure to selenium fumes hydrogen selenide or organic vapors will be manifested by

irritation of the conjunctivae and the mucous membranes of the upper and lower respiratory tract with engorgement, secretory activity and in some instances the development of a chemical pneumonitis. Acute sore throat has been reported in several instances.[2,3] Residual effects usually are short lived and similar to the symptoms of chronic intoxication. Lauer[1] cites his experience with a group of workers showing acute reaction to selenium fumes. In these cases respiratory tract irritation predominated with pain and burning sensation of the nose and throat, substernal burning, tightness of the chest, headache, dizziness and conjunctivitis also noted in varying degree.

Chronic Intoxication

Chronic occupational exposure to selenium products will be productive of a syndrome characterized by metallic taste in the mouth, a garlic like odor to the breath, nausea, vomiting, dizziness and extreme lassitude and fatigability. Nausea is quite common and may sweep over a patient suddenly, causing him to bolt from his work bench to vomit. The garlic odor of the breath is particularly noticeable and may be drawn to the patient's attention by family or associates before the onset of other symptoms. Fatigability may be unusually marked and the worker will insist that he is unable to carry on his usual working or extracurricular activities.

Pain in the abdomen and lumbar pain have been reported.[3] Dermatological manifestations are not uncommon, approaching in some instances a toxic necrosis.[4] Parathesia has been described as has been erythromelalgia and melanosis. Smith and Westfall[5] have noted the following symptomatological complexes in patients utilizing selenium bearing foodstuffs over a long period of time, bad teeth, icteroid discoloration of the skin, history of recurrent jaundice, vitiligo, asthma, sallow and pallid color especially in younger persons, dermatitis, rheumatoid arthritis, pathological conditions of the nails, cardio-renal disease. Some analogy may be drawn with chronic occupational cases although the connotation of chronicity will vary according to occupational or natural sources of intoxication.

A normal range of 0.0 to 15.0 micrograms selenium per 100 c.c. has been reported as the urinary excretory rate.[7] A number of common food substances (eggs, meats, cereals, milk) contain selenium in significant amounts with corresponding reflection in the urinary excretion. Hemoconcentration[8] has been noted in acute intoxication with a subse

quent hypochromic microcytic anemia, which is seen also in chronic intoxication. The cephalin flocculation test usually is positive in variable degree following acute exposure with the peak reaction in Lauer's cases[1] occuring two weeks after exposure with a subsequent gradual return to normal.

PREVENTION

Prevention of selenosis is dependent upon a realization of the inherent hazard and will require the proper utilization of mechanical exhaust systems, local and general, and competent medical control. All workers potentially exposed should be examined at periodic intervals giving careful attention to complaints referable to the respiratory tract, the gastrointestinal tract and the general sense of well being. Routine examination of the urine for evidence of absorption of selenium may be helpful, but distinction must be made between occupational and natural exposures in evaluating the urinary selenium level. Impervious gloves and aprons should be utilized when necessary to prevent skin contact and absorption, particularly when working with selenium oxychloride and methylbenzoselenazole, selenium dioxide and selenious acid. Rubber gloves are also penetrated by these products and dependence should not be placed on gloves for prolonged prophylaxis. Respirators may be necessary if mechanical exhaust cannot effectively reduce dust concentrations, and air line respirators should be used when maintenance or rescue work is necessary in atmospheres of volatilized selenium products. Employment applicants with pre existent respiratory, liver or arthritic disease should be protected or excluded from exposure to selenium compounds.

TREATMENT

Therapy has been directed toward deselenization with little success. Upon removal from exposure the patient will eliminate naturally through the urinary, respiratory and gastrointestinal tracts the excess of selenium which has entered the body. Bromobenzene[9, 10] has been suggested as a deselenizing agent and has in a few cases increased the urinary selenium excretion with amelioration of symptoms. However, the toxicity of bromobenzene itself would militate against its use, and animal experiments have not confirmed its deselenizing value. BAL[11] (2, 3 dimethylmercapto propanol) has been utilized experimentally with

animals These experiments would indicate that BAL is additive in toxic effect rather than helpful On the other hand Amdur[1] utilized BAL 2 5 mgm /kg body weight in deep intramuscular injection rather freely to hasten elimination of tellurium in several patients with little or no toxic effect and as she believed an increased elimination through the respiratory tract as the methylated telluride Her most urgent indication was the relief of the social ostracism occasioned by the alliaceous breath With the following regime she reported a cessation of the garlic emanations in eleven to fourteen days BAL 2 5 mgm /kg body weight every 4 hours for 6 doses every 6 hours for 4 doses and 1 dose in 24 hours as needed It is difficult to say whether there was an actual excretory increase due to the BAL although the patients reported a noticeable increase in the offensiveness of their breath Cullen and Gross[11] state however that BAL is ineffective against selenium Nevertheless because of the close relationship between tellurium and selenium one would be justified in drawing a therapeutic analogy and utilizing BAL in selenium intoxication if there seemed sufficient indication

Removal from exposure probably will ameliorate and eventually eliminate most if not all of the symptoms due to acute or chronic industrial exposure Recovery is rapid in most cases with no serious complaints persisting over 10 to 14 days The alliaceous breath however may persist for variable periods of time but is essentially an indication of continued natural elimination Lassitude and apathy may persist for 4 to 6 weeks following removal from exposure Chemical pneumonitis may necessitate the use of oxygen and chemotherapy prophylactically or therapeutically for secondary infection Spills of organic selenium compounds on the skin should be washed immediately with copious amounts of running water to prevent not only chemical burns of the skin but undue absorption which is rapid in such instances

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Industrial Lxposure

Prevention of systemic or dermatological effects due to silver and its compounds is largely dependent upon the use of proper closed systems and local and exhaust ventilation in plating operations and importantly the use of protective clothing where necessary and avoidance of prolonged use or contact with silver nitrate or organic silver preparations Once established it is almost impossible to eliminate the discoloration of the skin or mucous membranes arising from silver absorption Fortunately aside from the cosmetic difficulties there is little systemic reaction and present evidence would indicate that silver does not constitute an industrial exposure problem of serious significance

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XXI

SILVER

By RONALD F BUCHAN

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Silver has a number of uses and the element itself is used in the manufacture of electrical conductors ornaments tableware and jewelry Silver nitrate is used extensively in the process of silver plating, silvering mirrors and in the production of photographic emulsions laboratory reagents indelible ink mother of-pearl glass and as a therapeutic agent

ARGYRIA

Except for accidental or suicidal ingestion of quantities of silver nitrate which will occasion acute gastroenteritis, the usual findings in silver intoxication may be listed under the heading of argyria in which the skin or mucous membranes will assume a local or general silver grey or bluish grey discoloration due to the precipitation of absorbed silver Schwartz and his associates[1] state that the pigmentation is first apparent at the gingival margin a violet metallic sheen which does not disappear under pressure Organic silver preparations used medicinally may also occasion cutaneous argyria in addition to gastrointestinal argyria Hermann in a war-time review concluded that argyria was the only significant reaction to industrial exposure He suggests local injection of 1 per cent potassium ferricyanide and 6 per cent sodium thiosulfate as of dubious but occasional help in reducing pigmentation Hill and Pillsbury[3] describe a number of cases reported by various authors due to occupational exposure Harker and Hunter[4] in discussing a series of occupational argyria cases state that the generalized form is frequently associated with ophthalmological changes In their cases there is staining of the conjunctivae especially the inner canthus

Amdur[2] reports on 3 cises exposed to i volitilized tellurium copper illoy These pitients suffered from heidache epigistric distress metal lic tiste in the mouth ind illiceous breath There were no significint liboritory findings Meid ind Gies[3] in in eirly report remirl ed on the similirity of bodily reiction to tellurium selenium irsenic and intimony Arsenic 5 p p m in drinking witer his been suggested is i prophylictic meisure to prevent the effects of exposure to selenium ind tellurium This however would not seem to be the most suitable ipproich to prophylixis

Prevention is dependent upon engineering control methods with locil and generil exhiust of processes giving rise to volitile inorginic or orginic products isolition of such processes when necessiry ind substitution of i less toxic miteril if possible Personal hygiene em phasizing the use of protective clothing and gloves to prevent skin absorption is i necessiry importint fictor although Shie and Deeds[4] originilly felt thit the evidence is to sl in ibsorption wis questionable

There is no specific *therapy* ind treitment is symptomitic accord ing to the locil minifestitions upon removil of the patient from the noxious atmosphere or contict BAL (3 dimethylmercapto propinol) has been utilized to increise the excretory rate and may prove useful to overcome persistence of the more objectionible symptoms (see Se lenium) With removil from the intoxicint atmosphere the tellurium will be griduilly eliminited through the body fluids excreta and the lungs ind no residuil effects should be noted ifter two months

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XXII

TELLURIUM

By RONALD F BUCHAN

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Tellurium is used in copper refining coloring glass, refining lead and zinc and by rubber makers and photographic workers As a component of steel and iron products it may be found in the production of automobiles railroad and agricultural vehicles and various tools and instruments It increases the depth of chill in castings and is productive of a wearing surface resistant to the ravages of use

Industrial Intoxication

Like selenium tellurium may enter the body via the respiratory or gastrointestinal tracts and by absorption through the skin Tellurium dissolves easily in tissue fluids and as a consequence is subject to deposition in all organs and body fluids entering usually as soluble salts volatile hydride ore dust or the oxide Steinberg[1] and his associates state that it is excreted in the urine and feces and in the breath and sweat in the form of methyl telluride The presence of tellurium as a contaminant of selenium has been postulated as the cause of the garlic odor of the breath in selenium intoxication There are few clinical cases of occupational tellurium intoxication described in the literature However, as with selenium the experience in industry is probably greater than indicated by the volume of literature Toxic symptoms are quite similar to those found upon exposure to selenium viz metallic taste in the mouth alliaceous breath odor gastrointestinal upsets with anorexia nausea and vomiting and in acute exposure irritation of the respiratory tract

Incidence

J C Munch compiled in 1934 all the thallium poisonings published up to that time There were 778 poisonings with 46 fatalities most of them caused by therapeutic use 79 with 15 fatalities by accidental intake of rodenticides 6 suicides 2 murders Since this time 37 poisonings have been published There is only a very small number of industrial poisonings The poisonings caused by therapeutic use of thallium salts in particular induced much research and many animal experiments Buschke and Peiser[2] enumerated in their bibliography (1931) 395 articles Since that time at least 23 other articles have been published Nevertheless the mechanism of the effectiveness of thallium is not yet clear It seems that there is an effect on the endocrine and vegetative system (Buschke and others[3]) Many authors think that the true mechanism is unknown There are some very interesting facts children below 10 years of age tolerate the poison better than adults a single dose has a smaller effect than the same dose given in parts over a few days The alopecia does not extend to the so called sensory hairs to which belongs the median part of the eyebrows In order to be more complete we will give a clinical and pathological picture of the medicamentous poisonings before we discuss the industrial ones

Medicinal Poisonings

In the acute poisonings there are first diarrhea sometimes colic later obstipation If the dose is not so great these signs may not be so pronounced The chief complaints then are first pains setting in after several days sometimes two weeks and especially attacking the legs the calves the articulations of the toes and the soles Polyneuritis develops After two weeks the hair begins to fall out sometimes deafness dermatitis later motoric unrest confusion retrobulbar neuritis atrophy of optic nerve sleeplessness and death occur The autopsies showed (Munch[1]) marked liver and kidney changes, changes also in the peripheral nerves and the central nervous system (the pyramidal tract the third nucleus the globus pallidus) Schneider[5] also describes very exactly changes in the nervous system Thallium is excreted slowly and retained in the body for a long time L Goodman and A Gilman[6] close the chapter concerning thallium with the words a most unnecessary and dangerous drug

XXIII

THALLIUM

By LUDWIG TELEKY

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INTRODUCTION

Thallium is found in small amounts in pyrites (zinc pyrites iron pyrites or copper pyrites) and also in several brines Its smelting point is 300 C, its boiling point 1462 C There are univalents thallous salts and trivalent thallic salts The thallous salts are those which interest us from the toxicologic viewpoint Thallous salts are obtained from the residues of the treatment of zinc pyrites in order to obtain zinc These residues are extracted by hot water and acids and finally the thallium is obtained by electrolysis Thallium is used mostly in its salt form The poisonous thallous salts have been used for a longer time and in a greater measure in therapy principally for depilation in fungous diseases of the scalp ringworm disease in children which are epidemic in some countries and also as cosmeticum for epilation in the form of a French product Taly and in American one Koremlu Cream It was and is used also as rodenticide for killing mice rats prairie dogs and ground squirrels For this purpose Zeliopaste containing 5 per cent thalliumsulfate (each tube with 0 7 gm) and Zeliograins containing 1 6 per cent have been produced by I G Farben in Germany In U S A thalgrain has been produced, this is barley soaked with 1 per cent thalliumsulfate and it has been distributed in California by state authorities (Munch[1])

INCIDENCE

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MEDICINAL POISONINGS

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Industrial Poisonings

The number of occupational damages by thallium mentioned in the literature is small and even smaller is the number of those which have been observed by a physician.

There is a potential danger in obtaining thallium from the residues of the treatment of ores, in using thallium compounds for the manufacture of pharmaceuticals and rodenticides, also in the production of paints and glasses, especially of highly refracting lenses, imitations of precious stones, in extending the life of tungsten filaments of lamps, in pyrotechnical and in analytical laboratories (Heyroth). Furhill[8] points out the danger present in spectrographic analyses.

What is the real occurrence of occupational poisonings? Schneider mentions accidents in the production of paints and glasses. A. Buschke and B. Peiser report from a plant in chemical industry, which formerly used thallium, that a good deal of slight cases showing falling out of hair occurred years ago. The Prussian Ministry of Welfare made an inquiry throughout Germany at the instigation of Buschke[1]. It is mentioned repeatedly by Buschke, but cases detected in this way are not mentioned.

The cases described by Rube and Hendriks[9], S. Meyer[10] and Teleky[11] concerning the same patients are the sole occupational cases observed and described by physicians. They occurred in a factory in which thallium was obtained from residues, where there was a chance of inhaling small amounts of dust of metallic thallium, thallium oxide and thalliumsulfate. There were 14 workers so occupied in the course of about a year. In all of them excepting 3 complaints developed which caused absenteeism, first of all pains in the legs, especially in the knees. One worker after 3 months of work showed greatly increased patellar reflexes, slight conjunctivitis and then developed a considerable albuminuria with many erythrocytes in the sediment. This subchronic nephritis remained for many months after the worker had ceased to work, in fact for as long as he was under observation. The same kind of nephritis developed in another worker also. Some of the workers had a red coloring and falling out of hair. The leading engineer complained at the time of the first experiments of disturbances of sleep and one night had sensations of agitations and excitements. In all the workers lymphocytosis was found with always more than 40 per cent of lymphocytes and in those with nephritis more than 50 per cent. Lymphocytosis was found even after 4 days of work. Several of the workers showed eosinophilia. It may be stressed that there was no

parallelism between the blood findings and other signs or symptoms

Very serious signs have been observed in a worker 19 years of age Several weeks after beginning work though he had previously helped in the laboratory working with thallium he complained of severe pains in the legs which forced him to stay away from work for one and then for three weeks Diminution of the vision began after about 4 months of work progressing quickly The examination showed in the left eye posterior portion of the iris adherent to the anterior lens capsule From this adherent area an opacity of the lens developed In both eyes there was a discoloration of the optic papilla slowly progressive turning to pale on the temporal half The borders of the field of vision were normal but there was on both eyes a relative central scotoma for red and green Counting of fingers slowly diminished up to the distance of ½ meters the acuteness of vision was 2/60 That was a progressive atrophy of the optic nerve in consequence of a retrobulbar neuritis The patellar reflexes were absent and also the Achilles reflex of one foot There was no improvement of the nerve changes after many months of observation

In another thallium refining plant two workers worked with thallium only in intervals of several days and then for several hours only Neither of the workers had any complaints but they showed lymphocytosis one of them eosinophilia also

These cases show us the picture of the chronic occupational thallium poisoning the blood changes lymphocytosis and sometimes eosinophilia are signs of thallium absorption The symptoms of poisoning are pains in the muscles or the joints especially of the lower extremities redness of parts of the hair loss of hair atrophia nervi optici and other nervous symptoms

These are the only cases of occupational thallium poisoning observed by physicians and reported in the literature For the sake of completeness we may mention a case which happened in the motion picture industry A man (Jordan¹) came as a visitor in the laboratory in which experiments were being made with thallium in developing films Eating a sandwich he put it on a table which was contaminated by thallium sulfate He acquired serious thallium poisoning

Therapy and Prophylaxis

As to the therapy most of the authors report that the complaints disappear spontaneously The treatment can be undertaken only symptomatically For alleviating the pains luminal salicylates antipyrin

and warm baths have been recommended also (Karrenberg[14] Gettler and Weiss[1]) sodium thiosulfate (three times daily 1 5 gm by mouth) or intravenous injections of 0 6 gm sodium thiosulfate in 200 cc water E S Mazzei and F Schaposnik[16] gave in a suicidal case of a young girl daily doses of 300 mgm BAL up to a total of 2 85 gm in 13 days The patient recovered Also diuresis by drinking a large amount of liquids and purgation are recommended

For prophylaxis complete avoidance of dust is necessary, by the use of an effective exhaust system or by treating thallium in closed vessels and pipes Supervision of the workers by a physician including blood and ophthalmoscopic examinations is most important The examination must be performed in the beginning at least every 3 weeks after some months it may be performed at slightly longer intervals Every *worker showing the first signs of illness pains reddening of the hair should be transferred immediately to work in which thallium is not used*

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XXIV

VANADIUM

By RONALD F. BUCHAN

Vanadium is particularly used in industry for alloying with steel although it is utilized also in the processing of blue ink, glass and porcelain. It is also encountered in the extraction of ore and in salvage and reclaiming operations. There is a relative dearth of clinical information in the literature and consequently the symptomatology has been ill defined. In all probability the pentoxide of vanadium is responsible for the clinical picture which does develop.

Various authors have reported their findings from time to time and noted the following symptomatological complexes: irritation[1] of the mucous membranes with conjunctivitis, cough, varying degrees of expectoration and nasopharyngitis. Lower respiratory involvement has been manifested by the usual signs of subacute or chronic bronchitis. In these observations on 19 men, no gastrointestinal, renal, neurological or hematopoietic disturbances were noted. Gastrointestinal, neuromuscular and renal symptoms have been noted on one occasion but rarely since observed or confirmed. A syndrome with the following characteristics has been described by Wyers[3]: pallor of the skin, paroxysmal cough, rarely with hemoptysis, dyspnea, pains in the chest, barrel shaped emphysematous chest, profuse bronchitis, bronchospasm, reticulation on x-ray examination, greenish black discoloration of the tongue, raised blood pressure, accentuated pulmonary sound, palpitation on exertion, tremor of the fingers and arms. Sjoberg[4] suggests that the greenish black tongue discoloration arises as precipitation of quadrivalent vanadium hydroxides. He states that the action of normal sputum with alkaline pH is sufficient to produce the phenomenon, attributing to differences in manufacturing processes the difference in intensity and incidence of tongue discoloration when it arises. Malfino in animal experiments has described a severe irritation of the respiratory tract due to vanadium anhydride, stating that the after effects were similar to those experienced on exposure to zinc oxide. Later he relates with Balestra[6] their observations on workers exposed to petroleum ash containing vanadium, giving details of pulmonary lesions with some

resemblance to pneumoconioses This report is interesting in that it describes a hazard which is becoming more frequent Vanadium pentoxide is recoverable from stack deposits in ocean liners and freighters and commercial attempts at such salvage have emphasized the hazard Such operations are now being conducted in several East Coast ports

While no definitive epidemiological study has been made it would seem that upper respiratory infections and pneumonia have a higher incidence than in the general population X ray findings characteristic of bronchitis or pneumonia will be noted With the respiratory symptoms there will be a concomitant leucocytosis the degree dependent upon the severity of the process There is need for further definitive epidemiological study on vanadium exposures to supplement Symanski s observations

Sjoberg *has made a valuable and extensive clinical study of 36* symptomatic cases of vanadium pentoxide intoxication Characteristically manifested were irritations of the respiratory tract specifically the nose pharynx larynx and bronchi Affected workers complained of dryness and pain in the throat cough shortness of breath and palpitation on exertion weakness and fatigue Papular dermatoses were observed as were neurasthenic manifestations No gastrointestinal or hepatorenal disorders were noted Concurrent rabbit experiments con*firmed the human clinical observations* Short intensive exposures produced acute irritative changes of the respiratory tract and acute bronchopneumonia After recovery atelectatic and emphysematous residuals were apparent Chronic exposure to low concentrations initiated chronic inflammatory changes in the upper tract with bronchopneumonic and atelectatic progressions in the lower tract These latter findings have not been demonstrated in human cases

Prevention is dependent upon local and general exhaust control of any process giving rise to the emanation of dust or fumes of vanadium compounds particularly the pentoxide Where mechanical control cannot be utilized workers should wear dust respirators Personal cleanliness should be emphasized with frequent changes of work clothing

Therapy is non specific and directed toward amelioration of the local symptomatology of the upper and lower respiratory conditions

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XXV

ZINC

By RONALD F BUCHAN

Zinc is commonly encountered in the following industrial processes mining smelting manufacturing of brass and other alloys galvanizing and in a variety of incidental operations Suspecting zinc intoxication the examiner should inquire from the patient regarding the exact details of his work seeking information in regard to all components of materials with which he may work and the manner in which they are used The worker in many instances will not have this information and it may be necessary to turn to the plant management

The usual intoxication suffered from zinc is an acute syndrome known as zinc shakes metal fume fever or fume fever smelter's shakes or brass chills Ordinarily it is a transient phenomenon with no residual after effects The reaction is physiological with no demonstrable pathological changes For its discussion see XXVI on Zinc Fever by Teleky

A second common response to zinc exposure lies with the corrosive effects of its salts particularly the chloride on skin nails and mucous membranes Zinc chloride is utilized as a preservative of wood solder flux mordant in vulcanizing rubber in fireproofing textiles and in a variety of other operations Thus there is wide exposure Ulcers of the tissues and mucosa are encountered commonly They are quite similar to chrome ulcers deep and burrowing with a grey necrotic base There is little inflammatory reaction Schwartz and associates review an interesting series

Prevention and Treatment

Local and general exhaust control is necessary in order to obviate inhalation of the zinc fumes Modern industrial hygiene methods will eliminate toxic episodes and the appearance of zinc fume fever in a worker is indication of a serious gap in the engineering control methods. Those handling zinc chloride should utilize protective garments and gloves with daily changes of work clothes Nasal mucosa should be protected with vaseline

Chloride ulcers usually require curettage to prevent residual caustic action Alkaline lavage or dressing (powdered bicarbonate of soda) may be helpful followed by usual aseptic care

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XXVI

ZINC FEVER

Weaver's Fever, Dust Chills, Cotton Mill Fever

By LUDWIG TELEKY

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Historical

The famous sculptor Benvenuto Cellini (1500-1571) tells in his autobiography that in casting his work, the Perseus (1550), he fell ill with a high fever and thought that he was about to die. A few hours later the fever was gone and he continued his work. Perhaps this is the first description of founder's ague (Holtzmann[1]).

C. T. Thackrah (183) writes about the illness of brassfounders caused by inhalation of volatilized metal. The Frenchman Blandet (1845) reports the first experiments made on man in this field. Publications followed by the Frenchmen Becquerel (1845), Reboulleau (1847), Chevallier and Boys de Loury (1850) and the German Falck (1855) (quoted from H. Sifir[2]).

A very complete and extensive description of brassfounder's ague was given us by E. H. Greenhow in 186 [3]. This has not been excelled by later authors. Therefore we quote here some of his report: "The attack commences with malaise, a feeling of constriction or tightness of chest, sometimes accompanied by nausea. This always occurs during the

afterpart of a day spent in the casting-shop and is followed in the evening or at bedtime by shivering sometimes succeeded by an indistinct hot stage but always by profuse sweating The sooner the latter follows the setting in of the cold stage the shorter and milder is the attack * * * which at the worst is only ephemeral, but the attacks are sometimes of frequent occurrence Persons who have but lately adopted the calling or who only work at it occasionally and regular brassfounders who have been absent from work for a few days are more liable to suffer from this disease than those who work at it continually The men themselves attribute this disease to inhaling the fumes of deflagrating zinc and there can be no doubt that their opinion is correct * * * Brassfounders suffer from it in almost exact proportion to their liability to inhale these fumes'

Some of the conclusions drawn by this author are 'The severity and frequency of the attacks are much influenced by the regularity with which men work in the casting shops those who work steadily at the occupation appearing to acquire a tolerance of the poison which is however only temporary seeing that after a few days' absence from work even the most seasoned casters are apt to have an attack of the metal ague on being exposed to the fumes of the deflagrating zinc * * * The severity and frequency of the attacks depend mainly upon the quantity of zinc fumes evolved in the atmosphere of the casting shops those men who mix the metals and especially those who use a large quantity of zinc in their castings being much more liable to suffer than those who merely remelt brass bars or make brass containing but a small proportion of zinc Any cause which tends to retard the dispersion of the fumes into the atmosphere—such as a close ill-ventilated work shop or foggy weather or a high wind that beats back the fumes into the shop —increases the liability of the casters to suffer from metal ague * * * Operatives such as makers of galvanized iron ware who work over molten zinc below the temperature of deflagration enjoy an entire immunity from this disease

Greenhow gives the following further description If the molten brass is being poured into moulds the zinc deflagrates and a dense white smoke is formed which almost instantaneously fills the atmosphere of the casting shop This smoke is rapidly converted into snow-like flakes and white powder consisting of the oxide of zinc which remain for some time diffused through the atmosphere of the shop in ill ventilated casting places collects upon the rafters and ceiling in the form of a dense white incrustation

Since that time a very great deal has been written about zinc fever H Safir[3] enumerates in 193- 93 articles though he neglects the American literature Adding to these 93 articles the American and those since published there are about 130 publications in all but as Hegsted and associates[6] write they have brought little more insight into the mechanism of action and added only little concerning etiology and symptomatology to the description of the illness

Clinical Picture

In regard to the clinical picture it is very much stereotyped but as in every other disease there are light and serious cases and some slight variations Sometimes a slight enlargement of the liver rarely of the spleen is reported Leucocytosis up to 20 000 with prevalence of polymorphonuclear neutrophiles was first reported by Arnstein[7] in 1910 and confirmed by all the later observers Only rarely are changes in the red blood picture reported and then they are minor ones Tachycardia is mentioned often Light albuminuria has been found in a few cases The content of zinc in urine and feces which older authors thought important was later proved unimportant when Rost[8] demonstrated that the normal daily amount in the urine is 1 to mgm of zinc with 19 to 39 mgm in the feces

Atypical cases are reported by the Russians Guelman[9] and Iwanow[10] who describe more serious cases with enlargement of the liver and spleen clear diminution of the red blood cells and of the hemoglobin no clear leucocytosis but an increased number of lymphocytes Guelman mentions also glycuria and hyperglycemia Their patients seem to work under especially unfavorable influences or are exposed to other noxious conditions also Greenhow saw a founder with paralysis agitans and reports that in one factory nearly all the founders became more or less shaky possibly this resulted from the addition of mercury Graeve[11] reports a man who eight days after an attack of brass ague died suddenly after a strong physical effort but it does not seem justifiable to suppose a connection between the fever attack and the death

Incidence

There are many attempts in the literature to solve two questions One question is How many of the exposed workers fall ill Here we

are dependent entirely on the subjective statements of the individual workers. About 80 per cent of the workers in interviews said that they had suffered attacks of brass ague once or several times.

H. Natvig[1] found in his investigation of 100 brassfounders, working several months up to 60 years, that 12 had zinc fever once, 24 2 to 10 times, 28 11 to 100 times, 36 more than 100 times. Turner and Thompson[13] report that among 100 brassfounders 26 had brass ague once a week, 11 once in 2 weeks, 29 once in 3 weeks up to 2 months, 17 per cent once a year, 6 once in 2 years, 1 once in 3 years. Other authors report that some workers fell ill when exposed to the fumes the first time, others after exposure of a few days or some time later.

All such statements have much less significance than it seems at first sight because in relation to the development of an attack it is not sufficient to note that the man was exposed, the amount of concentration and the length of time are the important factors. Both these circumstances explain a good many of the differences between the workers. I would think that statements about those who never had brass ague, are due in great part to lack of memory.

Acquired Resistance

However it may be said with certainty that nearly all the workers after one attack acquire a certain resistance which seems to be maintained by *further inhalation for a shorter or longer time*. In this way only can be explained the fact that many workers fall ill again when they interrupt their work for a short time ("Monday fever") or after a longer interruption but have no complaints during uninterrupted work. Philip Drinker and associates[14] showed in experiments on men that a second inhalation on the day following the first had a lesser effect.

Another question is: Does an exposure for years with always repeated attacks of zinc fever provoke a permanent damage? Is there in addition to the acute damage a permanent or chronic one also? It is stated that there are no characteristic damages of organs, that such do not appear in the many foundries with far from good conditions.

Relation of Zinc

Turner and Thompson[13] compared clinically 102 foundry workers having brass ague in the case history with 110 others not exposed

H. Natvig[13] compared 35 workers who had had more than 100 attacks with those having had less than 10 attacks. These authors came to the conclusion that definite illnesses or chronic sequelae of brass ague could not be stated.

In relation to the brass ague Thakrah had already seen its cause to be in the zinc fumes and so did all the following authors, but K. B. Lehmann[18] 1910 first proved it scientifically, making himself and several workers inhale the fumes of chemically pure zinc which had been melted, heated further and then burned. The characteristic picture of brass ague developed in everyone undergoing the experiment. The fumes given off by the zinc heated above its melting point before they come in contact with the worker are instantly oxidized by the oxygen of the air. No metallic zinc nor zinc superoxide could be found in the zinc oxide dust collected in the foundry.

Greenhow had already explained why zinc fumes are generated in such a great amount. In melting pure zinc (melting point 4[illegible]0° C) the temperature is not raised to the sublimation point, but sublimation *occurs when zinc is mixed with copper and heated up to the melting* temperature of this metal (about 1300° C). The more zinc the brass contains the more zinc is volatilized in melting. The "yellow brass" contains the greatest amount of zinc, up to 40 per cent, according to Hayhurst[1] even up to 50 per cent zinc. Other kinds of brass contain zinc in diminishing amounts to 18 per cent, tombac and red brass less than 18 per cent; alpacca or german silver contains besides copper and nickel 15 to 20 per cent of zinc. All these alloys may cause brass ague in melting. Besides the percentage of zinc in the alloy the temperature up to which it is heated will be different depending on the purpose; for casting smaller parts the alloy has to be hotter in order to be more liquid (Gerbis[1]).

Of the greatest importance are, of course, the circumstances in the workshop. How large is the room, how it is ventilated, what amount is cast in the room? In some small foundries casting is done in one place only under an exhaust hood; in most foundries casting is done in the whole casting room and a ridge turret or artificial ventilation takes care of exhausting the fumes. The quick removal of zinc fumes is the most efficient method of preventing brass ague.

It is self evident that not only in casting but everywhere that zinc is volatilized and inhaled, zinc fever may arise. This applies to the production and use of hard solder, an alloy of brass and more zinc or other metals (A. Hamilton[19] 1919, J. Adler-Herzmark[20] 1921, Beintker[1] 1933).

Numerous cases of zinc fever have been caused by the growing use of oxyacetyline and electrical burners in welding and cutting J W Hammond and Gerbis[3] report cases of zinc fever from the cutting of zinc which was formerly cast or flowed into cavities

Very numerous and important are the zinc fever cases caused by autogenous or electric welding or cutting 'galvanized iron or steel Galvanized' means protected against rusting by a layer of zinc In galvanizing covering iron or steel with zinc, no zinc fever arises because the zinc is not overheated (according to McCord[4] up to 468 C) and its surface is protected partly by amonium chloride partly by charcoal and other material The use of galvanized material and of welding and cutting it by electro or oxyacetylene-burners is increasing in the construction and dismantling of iron and steel structure especially ships Therefore there are reports about zinc fever by many authors (Hayhurst 19-4 Lominack[6] 1943, Session[7] 1944 and Drinker and Nelson[8] 1944) Hence the names '*galvochills*" or "*galvanizing poisoning*' Rarely are reports about fever in cutting sheet metal painted by zinc white (Beintker[29] 19 2/-3)

In *metal spraying* with Schoop pistole the zinc wire entering it is melted by a gas oxygen flame and then sprayed Workers doing such work suffer sometimes from zinc fever (Nuck[30])

We have just now spoken of zinc oxide in statu nascendi but Ph Drinker and coworkers[31] 1927 have shown in self experiments that fever can be caused also by other very fine zinc oxide powder Such cases out of the industry are reported by Nuck[3] and Turner and Thompson[13] Gocher[33] writes that zinc chromate used for painting may cause zinc fever but as a whole it seems to me that there have to be special circumstances for zinc oxide powder or other zinc compounds to cause chills

It is remarkable that in *zinc smelters*, producing zinc from zinc ores there is very little reported concerning chills and nothing from the big smelting works in Upper Silesia Since economically it is very important that no zinc is volatilized there the experts have been experimenting for a century and as a result for the last fifty years a certain type of furnace has been used in which a system of two condensers avoids the escape of zinc fumes out of the furnaces It seems not impossible that using older types of furnaces zinc fever may be generated Such cases were reported in 1913 by Hayhurst[17] from Illinois and were seen by myself[34] On the other hand chills occur also in the most modern systems in which zinc ore is distilled by high tension currents (Teleky[18]) When in such a plant the filter installation became defec

tive in November 19 0 and was in repair there developed zinc fever like an epidemic among the workers In the following years chills occurred temporarily especially in bad weather

After all a specific acute feverish illness is generated when zinc fumes or fogs of ZnO are inhaled whatever source they come from The particles of zinc oxide fumes are below 1μ mostly 0.1 – 0.4μ but they aggregate quickly Ph Drinker[3] through his research came to the conclusion that 14 mgm of zinc oxide in a cubic meter of air even inhaled for 8 hours produced no reaction in the average subjects Different authors found different amounts of zinc oxide in the air Arnstein[4] found 7 mgm of zinc oxide in 30 liters of air in a brass foundry during casting As the men inhaled about this amount of air during casting and then fell ill he thinks that 7 mgm sufficient to cause zinc fever Hegsted and associates the California Industrial Commission and the New York and the Massachusetts Division of Industrial Hygiene accept 15 mgm in a cubic meter as the allowable limit

Relation of Metals Other than Zinc

All that has just been described refers to zinc and up to some time ago the fever was commonly called zinc fever or brass ague but there are now several publications offering exactly the same clinical picture in men inhaling dust of copper or copper oxide as causing copper fever Hansen[38] in reporting in 1911 on 10 workers who were occupied in melting 2300 kg electrolytic copper scrap in a standard three phase arc furnace states that all 10 fell ill with symptoms like brass ague Koelsch[37] reported in 19 3 on 10 workers in a rolling mill in which red hot copper was rolled At the end of the working day they fell ill with all the symptoms of brass ague The observations of Koelsch confirmed the reports of the workers The cases described by L Triberg and E Trysin[35] and E H Schiotz[3] are by far not so clear However based on the reports of Hansen[6] and Koelsch[3] it seems certain that a copper fever exists

The cases of pretended *iron fever* are not so well founded by far It cannot be excluded that several of the ill workers welded galvanized iron (Schiotz[3] Holstein[40]) one author (Lindus[41]) reports a case caused by treating a saw with emery but this seems improbable

The cases of *mercury fever* (Kisskalt[41] Bing[1] L M Carpenter and F G Benedict[1]) are cases with organic changes partly seen in autopsies and fever

Magnesium fever has never been seen in industry, and in the experiments of Ph Drinker[31] only one man's temperature mounted up to 37 ·8 C No one of the four men shows a typical clinical picture similar to zinc fever (chills)

For '*lead fever*' Safir[1] mentions three authors of which I am one, there is no quotation of the sources but I can say that I never saw lead fever

Summarizing There is no well founded basis for assuming the existence of other metal fevers than zinc fever and as a rare event copper fever

Therefore, I think that it is best to retain the old phrase 'zinc fever The phrase metal fumes fever is very easily conducive to a generalization which just now has no real basis

Cause of the Fever

In what way does the feverish reaction through the inhalation of zinc oxide come about? K B Lehmann[16] through his research came to the conclusion that the resorption of the content of cells out of the respiratory tract bacteria as well as epithelium cells which have been killed by zinc is the fundamental cause of the illness of zinc fever L Schmidt Kehl[16] 19-8 tried to support this conception by ingenious experiments Rabbit's serum completely sterile was exposed to zinc oxide fumes then freed from zinc oxide by centrifugation it was injected into healthy rabbits Fever was produced in them It may be that the zinc oxide changed the albumen of the serum in such a way that it produced fever

At the present time no better explanation than this resorption theory has been found Kuh and associates[17] pointing to the inquiries concerning cotton fever mentioned a little later on write (1946) It appears not unreasonable therefore to say that the presence of finely divided and dispersed metallic oxide in the lungs destroys the microorganisms of the lower respiratory passages thereby liberating endotoxins into the alveolar capillaries and causing an acute febrile response Once this sterilisation has occurred it renders the lower respiratory radicles 'immune to further fume exposure until sufficient time has elapsed for the reaccumulation of organisms '

Therapy and Prophylaxis

Concerning the therapy very little need be said The attack disappears by itself after finishing its typical course For relief the patient

should be kept warm and if there is no vomiting given warm liquids in small doses

For prophylaxis it is important in casting to heat the alloy no more than necessary to do pouring in well ventilated shops and as far as possible below special exhaust appliances If cutting or welding is done in narrow spaces air should be blown in and exhausted

Respirator masks are always makeshift The masks have to be well fitted but then they are of correspondingly greater nuisance poorly fitted they are without any value The usual dust masks are in every case without any value metal fume respirators are necessary When zinc is used for spray painting the airline respirator is indicated

Weavers Fever Dust Chills Cotton Mill Fever

For many years ailments known as weavers fever dust chills or cotton mill fever have occurred in the cotton industry and similarly in hemp jute and flax industry Their nature was not clear

W L Ritter and A A Nussbaum[1] described in 1944 an illness which previously had received practically no attention from physicians but which is well known to all foremen in the factories in which there is much cotton dust in cotton seed oil mills as well as in textile and mattress factories Ten to fifty per cent of the newly employed workers develop chills on the first day of work sometimes in the factory but mostly after returning home The fever reaches 38° to 39° C with nausea headache and sometimes nosebleeds The symptoms nearly always disappear by the next day but are repeated on the following days at which time the attacks become less severe When the worker stays from work for two weeks then the more marked symptoms develop again These descriptions of cotton fever are so completely identical with those of metal fume fever as to suggest the conclusion that they have an identical pathology

In the cotton dust of factories in which this illness has appeared Neal and associates[1] found a bacterium *Aerobacter cloacae* which they found in great masses also in their research concerning an illness of mattress workers using the same kind of cotton and suffering similar but not identical symptoms Their conclusion based on thorough research was that an endotoxin caused by this bacterium produces the illness This is an explanation which is to a certain degree similar to that given above for the same clinical picture after inhalation of zinc oxide So the

statements of Neil concerning cotton fever seem to confirm the statements concerning zinc fever For prophylaxis in connection with these fevers large rooms sufficient ventilation and dust respirators are necessary

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XXVII

CYANIDES

By Adelaide Ross Smith

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Introduction

Compounds of cyanogen (CN) commonly spoken of as cyanides are frequently used in industry although they are among the most toxic of known substances In spite of this cases of industrial cyanide poisoning are relatively rare

Most commonly encountered in industrial use are the sodium potassium and calcium salts of hydrocyanic acid and the volatile cyanogen compounds The latter include hydrocyanic acid itself cyanogen chloride and the organic derivatives of cyanogen i e the various nitriles acetonitrile propionitrile etc

Industrial Uses

Cyanogen compounds have a variety of uses In the chemical industry they are used as reagents and for organic synthesis in the manufac

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through their ability to combine with the catalysts containing iron or sulphur in the tissue cells Thus they produce cellular asphyxia in the presence of oxygen Removal of cyanide allows the return of normal function provided death has not intervened in the meantime Hydrocyanic acid combines with difficulty with hemoglobin but readily with methemoglobin to form cyanmethemoglobin a fact which is utilized in modern therapy for cyanide poisoning

Independent of their general toxic action cyanides exert an irritating effect on the skin and mucous membranes

Permissible Concentrations

Henderson and Haggard[1] give the following table of physiological responses to varying concentrations of hydrocyanic acid

	Parts HCN per million parts of air
Maximum concentration allowable for prolonged exposure	20
Slight symptoms after exposure of several hours	20 40
Maximum concentration that can be inhaled for 1 hour without serious consequences	50 60
Dangerous after exposure of 30 minutes to 1 hour	100 240
Fatal after exposure of 30 minutes	200 400
Rapidly fatal	3 000

It is the rule of the United States Public Health Service that an experienced workman may enter a room after fumigation if the air contains no more than 100 parts of HCN per million of air

Acute Poisoning

Symptoms and Signs

Acute cyanide asphyxia is one of the most rapid known modes of death In the ordinary case the individual falls after a few breaths or even a single breath of the contaminated atmosphere Breathing may continue for a brief period and during this time it is greatly increased in volume but death often follows almost immediately

Patients who have narrowly escaped death report their preliminary symptoms as constriction of the throat dizziness fullness of the head

ture of drugs, perfumes etc, and also in the manufacture of various chemicals disinfectants, dyes, fertilizers and explosives Other work which requires the use of cyanogen compounds, but in which the liability to poisoning is slight, is electroplating the extracting and re fining of gold and silver the silvering of mirrors, the making and using of mordants, in certain forms of photographic work and in the spraying of trees

The process of hardening the surface of iron or steel by heating it with sodium cyanide is one used extensively in industry but there is little evidence that this process causes cyanide poisoning except contact dermatitis The commonly used sodium and potassium ferri and ferro-cyanide are relatively non poisonous unless acted upon by strong mineral acids which may then liberate hydrogen cyanide This will occur from the action of such acids on any of the common cyanide salts

Hydrogen cyanide is the most highly toxic of all cyanogen com pounds It is extensively used in exterminating vermin rats mice and moles This is done by generating hydrocyanic acid gas in the enclosed space requiring fumigation through mixing a cyanide salt usually potas sium cyanide, with sulphuric acid The greatest danger attending this process is that a worker may enter the room or enclosed space before the poisonous gas has been dispelled Hydrogen cyanide may be liberated also in poisonous quantities by the burning of celluloid and nitrocellulose films

Acrylonitrile or vinyl cyanide is a commonly used organic cyanogen compound which plays an important role in the production of the synthetic rubber known as Buna N

Mode of Entrance to the Body

The outstanding portal of entry to the body of the cyanides in industrial exposure is the respiratory tract although it is important to realize that acrylonitrile and hydrogen cyanide can be absorbed also through the skin, especially if breaks in its continuity are present

Action on the Body

The cyanides are true protoplasmic poisons arresting the activity of all forms of animal life They act by the inhibition of tissue oxidation

through their ability to combine with the catalysts containing iron or sulphur in the tissue cells Thus they produce cellular asphyxia in the presence of oxygen Removal of cyanide allows the return of normal function provided death has not intervened in the meantime Hydrocyanic acid combines with difficulty with hemoglobin but readily with methemoglobin to form cyanmethemoglobin a fact which is utilized in modern therapy for cyanide poisoning

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Acute cyanide asphyxia is one of the most rapid known modes of death In the ordinary case the individual falls after a few breaths or even a single breath of the contaminated atmosphere Breathing may continue for a brief period and during this time it is greatly increased in volume but death often follows almost immediately

Patients who have narrowly escaped death report their preliminary symptoms as constriction of the throat dizziness fullness of the head

nausea and vomiting Some of these patients then have gone into convulsions Examination reveals the eyes to be glassy and staring with dilated pupils The body is covered with cold sweat and frothing at the mouth occurs, often bloodstained Respiration is slow and shallow Involuntary defecation or urination is common For a time there may be complete paralysis If recovery occurs usually there is headache drowsiness and difficulty in speaking As with all asphyxiants a transient glycosuria is not uncommon A rosy red color of the skin usually is present although varying degrees of cyanosis have been observed This rosy color is due to the fact that oxygen has not been removed from the blood by the tissues and venous blood remains therefore in the arterial state An odor of cyanide on the breath described as the odor of bitter almonds is noted sometimes

Chronic Poisoning

Chronic poisoning is rare but may result from exposure to small quantities of cyanides over a long period of time Symptoms may be related to the digestive muscular or nervous system Weakness dizziness headache loss of weight loss of appetite nausea, vomiting muscle cramps unsteady gait and paralysis of arms and legs have been reported Polycythemia is found occasionally

Wilson reported that in synthetic rubber plants mild exposure to acrylonitrile may cause nausea vomiting weakness headache diarrhea jaundice and anemia According to Reed[3] irritation of the skin with conjunctivitis edema of the eyelids and lachrimation frequently appears in those continuously exposed to cyanogen chloride

Disability

In the acute surviving cases disability usually ceases with the disappearance of the symptoms which ordinarily do not last longer than one or two weeks In less severe cases symptoms cease within a few days In chronic cases recovery may occur within a week or so following the removal of the patient from the hazard but in some instances considerably longer disability may result Smith[4] cites one case of mild acute poisoning in which disability lasted for six weeks and two cases of chronic poisoning with continuing disability after one year and three years respectively

Diagnosis

Cyanide poisoning is diagnosed on the presence of characteristic symptoms and signs plus a history of exposure to cyanogen compounds

Examination of blood or gastric contents for cyanide may be made by the following method

1 To about 10 c c of the suspected fluid (blood or gastric contents) add two drops of 10 per cent sodium hydroxide c c of 1 5 per cent ferrous sulfate and 1 c c of 10 per cent ferric chloride Warm mixture and cautiously add 10 per cent hydrochloric acid avoiding excess A blue precipitate (potassium ferro cyanide) shows the presence of a cyanide compound

To examine blood for cyanide dissolve 10 mgm of ferrous ammonia sulfate and 10 c c of ammonium acetate (5 to 10 per cent) in 50 c c of water If 1 c c of this solution is added to a small amount of blood containing cyanide a purplish precipitate occurs

Treatment

Preferred modern methods of treating acute cyanide poisoning follow the work of Chen Rose and Clowes and depend on the immobilization of cyanide through the formation first of methemoglobin and subsequently of cyanmethemoglobin On the basis of animal experimentation these authors recommend the following procedures

1 Immediate administration of amyl nitrite for 15 to 30 seconds Repeat every 3 to 5 minutes if patient is unconscious and rigid
Gastric lavage at once if cyanides were taken by mouth preferably done by another physician to save time
3 Artificial respiration manually in case of gasping while amyl nitrite is being administered
4 Frequent counting of pulse and respiration rates
5 Continuous observation of patient for at least the first 4 hours During convulsions the inhalation of amyl nitrite may be prolonged to a minute or longer When respiration and heart rates show little or no abnormality administration of amyl nitrite may be reduced to once every several hours

To combat severe headache use an analgesic with no depressive action on the respiration

Ingegno and Franco[6] report the successful treatment of two serious

acute cases in human beings They recommend the following procedures, which are very similar to those of Chen Rose and Clowes, but include the administration of sodium thiosulphate This is given to help in immobilizing the cyanide through the formation of sodium sulfocyanate

1 Artificial respiration and stimulation
2 Amyl nitrite inhalations
3 Intravenous sodium nitrite (0 3 gm in 10 c c water) at the rate of 2 5 to 5 c c per minute
4 Follow immediately through the same needle with sodium thiosulphate (25 to 50 c c of a 50 per cent solution) at the same rate
5 Gastric lavage if cyanide has been taken by mouth using 3 per cent hydrogen peroxide or 0 2 per cent potassium permanganate
6 Repeat ½ dose of the antidotes in 1 hour if signs persist May be repeated again in 2 hours
7 Observation for 24 hours

PREVENTION

The prevention of cyanide poisoning depends upon a knowledge of the toxic potentialities of the cyanogen compounds together with care in maintaining adequate personal protection This can be achieved by means of suitable garments which will prevent contact with the skin and by the use of respirators where necessary

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CARBON MONOXIDE

By W. F. von Oettingen

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Introduction

The dangers of carbon monoxide poisoning are closely linked to the history of civilization they have considerably increased through the ages with the introduction of illuminating gas for domestic use the introduction of the combustion motor and the development of various industries in which carbon monoxide may be encountered For this reason the subject of carbon monoxide poisoning its hazards and the mechanism of its action has been reviewed repeatedly in monographs and reference should be made to the publications of Lewin[1] Sayers and Davenport Drinker[3] and von Oettingen[4]

In the following pages an attempt has been made to summarize and discuss the various aspects of carbon monoxide poisoning the mechanism of its action and the methods suggested and practiced with regard to the treatment of carbon monoxide poisoning

Chemical Properties and Chemistry of CO

Carbon monoxide CO has a molecular weight of 8 01 a specific gravity of 0 814 at $\frac{-195}{4}$ C or 0 9671 (air = 1) and a density of 1 2504 gm per liter (at 0 C and 760 mm Hg) It is a colorless and odorless gas except in high concentrations (75 or 100 per cent) when it has an appreciable garlic like odor (Sayers and Yant[5]) It melts at −207 C and boils at −192 C and its solubility in water decreases from 3 5 volume per cent at 0 C to 1 5 volume per cent at 60 C It may be absorbed by dusts as for instance by coal dust and it may be liberated again under certain conditions At 650 C it burns with a blue flame which is extinguished in air containing less than 13 4 per cent O but it does not support combustion Its explosive limits are between 12 5 and 74 volume per cent CO in air (Coward and Jones[6])

Carbon monoxide is a toxic gas Its toxic effects are to a certain extent the same as those produced by anoxemia because it combine with the red pigment of the blood (hemoglobin) and prevents in thi way the absorption and transportation of oxygen to the tissues of the organism

Sources of Exposure to CO

In accordance with the wide distribution and the frequent occurrence of CO as a product of incomplete combustion of coal or organic (carbon containing) materials the hazards of CO poisoning exist in many industrial operations and also in our daily life These hazards have been discussed repeatedly and more recently by Lewin[1] Sayers and Yant[5] Sayers and Davenport[2], Dublin and Vane[7] and Mayers[8]

In the chemical industry CO hazards exist in many operations This holds true especially for the manufacture of ammonia gas according to the procedure of Haber and Bosch the synthetic production of methane and methanol and the manufacture of soda with the Le Blanc process Charcoal burners and carbide workers also may be exposed to CO CO hazards exist also in the manufacture of illuminating gas where coke oven workers and tar distillers may have a severe exposure

In the metal industry the blast furnace workers Bessemer furnace men and welders (acetylene) are exposed to CO and CO hazards exist also in the smelting of copper, lead silver and zinc and in foundries (chargers cleaners core makers and cupola men) Blacksmiths plumbers and solderers also may have exposure to CO In the garment industry felt blockers and flangers calico printers cloth singers ironers and pressers may have exposure to CO In the ceramic industry kiln workers and brick burners appear especially to be exposed but some exposure exists also for teazers temperers, mold makers enamel makers and enamelers

In the mining industry the main hazards appear to result from fire damp explosions but the gases of explosives may also contain more or less high concentrations of CO so that blasters may have a quite heavy exposure In the electric industry CO hazards may exist for cable splicers and the makers and sealers of electric bulbs

CO constitutes an industrial hazard in a number of other industries Linotypists and monotypists using melting pots may be exposed to CO Chimney masons and chimney sweeps may be exposed while repairing and cleaning chimneys if these have not been properly ventilated previously CO hazards exist also in those industries which use ovens and stoves of different types Here the personnel attending the furnaces such as firemen and boiler cleaners are especially exposed Cooks and bakers may develop CO poisoning if their ovens are not properly constructed or operated Considerable exposure to CO may exist also in those trades which are connected with the automotive industry as for instance garages and repair shops

The importance of CO as an industrial poison is also illustrated by the report of Bridge (Editorial Safety Engineering[9])

Determinations of the amount of CO in gases from various sources under various conditions as published by Sayers and Yant[5] are summarized in Table I

TABLE I

CONCENTRATIONS OF CO IN AIR FROM VARIOUS SOURCES AND UNDER DIFFERENT CONDITIONS

Type and Source	*CO volume per cent*
Mine explosion immediately after dust explosion (exptl) as found in mine air	8.0
Mine explosion 1 day after explosion in coal mine	1.0
Mine fire as found in mine air	1.0
Blasting with 40 percent gelatin dynamite 7 minutes after shooting 100 sticks as found in mine air	1 2
Blasting products of combustion from black powder	10 8
Products of combustion of 40 percent nitroglycerine dynamite (gas diluted with air)	18 0
Products of combustion of 40 percent ammonia dynamite	5.0
TNT (gas produced undiluted with air)	60.0
Blast furnace stack gas (undiluted with air)	28 0
Bessemer furnace gas (undiluted with air)	25.0
Crucible furnace gas fuel melting Al Cu Sn alloy (undiluted with air)	5 5
Arc furnace (melting aluminum undiluted with air)	32 1
Cupola gas (undiluted with air)	17.0
Coke oven gas (undiluted with air)	6.0
Coal gas (undiluted with air)	16.0
Carburetted water gas (undiluted with air)	30.0
Blue gas water gas (undiluted with air)	40.0
Producers gas from coke (undiluted with air)	25.0
Producers gas from oil (undiluted with air)	5.0
Distillation of coal oil mixture (undiluted with air)	7.4
Gas range burning natural gas (improperly constructed and operated appliance diluted with air)	0 1
Room heater natural gas (improperly constructed and operated appliance diluted with air)	0 5
Automobile exhaust gas from exhaust pipe approximately 1 to 12.0 average	7.0
City fire (black smoke from burning building)	0 1
Insulation burning in electric arc	0 5
Furnace gas from solid fuel fired small house heating hot water system	1.0
Railroad locomotive stack gas	2.0

The oldest source of CO poisoning came with the use of fire by man and since time immemorial the fumes from burning fires regardless of

whether or not these were open, in portable stoves and braziers or in installed ovens and furnaces, have taken their toll among all classes of the population The literature on this subject is considerable and has been covered adequately by Lewin[1] and Sayers and Davenport

The amount of CO generated by any type of fire is dependent largely upon the amount of O available for the combustion From the report of Selter and Frankenstein[10] it appears that, in the case of charcoal fires at least, the amount of CO formed does not vary considerably during the initial firing and the subsequent glowing, as had been claimed by other investigators Haldane and Makgill[11] claimed that wet coal will form less CO than dry coal under the same conditions In addition smoke from burning structures and buildings may contain many other gases besides CO such as nitric oxide and hydrocyanic acid so that the clinical picture of poisoning from inhalation of such smoke may vary considerably Numerous other factors may enter the picture of CO poisoning from coal or other fire fumes The older literature abounds in reports of such poisonings, which were caused by shutting off the draft of ovens and furnaces in order to save fuel and maintain heat, others could be traced to faulty construction of the stove or flue Such accidents have occurred in recent years especially in buildings such as churches the heating plants of which are used only at intervals CO poisoning also occurs occasionally from the use of primitive coke ovens such as those used for drying buildings and for heating rivets and soldering irons especially when these are set up in small enclosures It should be remembered that under such conditions CO may accumulate in the upper sections, especially if there is no circulation of air

A great number of accidents from inhalation of CO have been reported from the use of portable wood charcoal pans for warming rooms such as those still used in the southern countries of Europe

The commercial and domestic use of *illuminating gas* as fuel and for illumination may be a source of considerable CO hazard As pointed out by Hubner[12] most cases of occupational illuminating gas poisoning occur not in the plants where the gas is manufactured but chiefly during the installation and repair of gas pipe lines Within the plant only the attendants of the scrubber and to some degree the firemen appear to have a definite exposure This appears to be substantiated by the report of Kerr[13] on the results of examination of gasworks employees in Greater Melbourne Australia Although 15 41 per cent of the men examined were found to show evidence of absorption of small quantities of CO the average absorption apparently was not large enough to cause

specific symptoms or serious after effects In only a few instances was there evidence of exposure as indicated by an increase in the number of red blood cells and hemoglobin

As pointed out by McCombs[1] accidents caused by illuminating gas itself may be divided into 2 classes They may be caused by a direct break in the gas lines within a room or failure to close a gas jet They may also result from leakage or the breaking of a main in the street by frost or other causes When the ground is frozen the gas travels along the pipe lines and ultimately escapes into dwellings

Although the toxic properties of illuminating gas are mainly due to its content of CO it has been claimed repeatedly as for instance by Ferchland and Vahlen[3] that illuminating gas is more acutely toxic than its CO content would indicate because other constituents for instance unsaturated hydrocarbons may be contributing factors In addition the CO content of different types of illuminating and industrial gases may vary greatly According to McNally coal gas may contain between 5 and 10 per cent water gas 30 per cent and producer's gas from 20 to 30 per cent CO

The concentrations of CO in air from different *domestic appliances* may vary considerably with their type and method of handling Jones Berger and Holbrook determined the quantity of CO accumulated in a closed room of 1 000 cu ft capacity when a natural gas burner was burned until the flame was extinguished as being from 0 to 1.72 per cent Koelsch found concentrations below 0.01 per cent in large kitchens in which gas ranges were used In smaller kitchens especially if the flame of the range impinges upon a cooling surface such as wash boilers it may be considerably higher as indicated by the report of Meyer[8] who found concentrations of 0.03 to 0.04 per cent When a yellow flame was used it increased to as much as 0.582 to 0.73 per cent Poorly constructed oil stoves may produce considerable quantities of CO as pointed out by Reuter[79] The amount of CO produced by different types of flatirons may be quite considerable Charcoal flatirons produce as much as 0.13 to 0.20 per cent CO (Meyer) coke flatirons as much as 0.093 per cent (Koelsch) and gas flatirons as much as 0.0078 to 0.01 per cent (Meyer[1])

In laboratories of different types considerable quantities of CO may result from the use of gas appliances if the air is not replaced by proper ventilation Egdall stated that in a laboratory where 16 Bunsen burners were operated the air contained at the end of 2 hours 0.1 per cent CO Jusatz and Nolte found concentrations of 0.016 per cent CO and in

one instance 0.024 per cent in 24 out of [illegible]08 tests made in various laboratories. In another laboratory, which was heated by a defective gas stove the concentration was as high as 0.073 per cent (Schick[23]).

Incidents of CO poisoning from domestic gas appliances are not uncommon as shown by the reports of Jones and Yant[24] and others. Jacoe reported several cases of CO poisoning resulting from exposure to CO contaminated air coming from the vents of domestic refrigerators.

Another very important source of CO poisoning was created by the introduction and ever increasing use of the *automobile*. The CO hazards for drivers and riders in automobiles as result of exposure to exhaust gases has been discussed repeatedly, and serious and even fatal poisonings from such exposures have been reported. The concentration of CO at the level of the driver was determined by Van Deventer[5] and the California State Department of Public Health.[7] The former found dangerous concentrations of 0.03 per cent CO in about [illegible] per cent of the automobiles tested and according to the latter 3 per cent of 1 00[illegible] cases tested showed higher concentrations than 0.01 per cent CO.

As pointed out by Jones and Katz,[8] during the summer months when doors and windows are open natural ventilation may be sufficient to prevent dangerous concentrations of CO in *private garages* but in the winter time this has to be supplemented by artificial means. A report by Yant, Jacobs and Berger[9] illustrates the rapid accumulation of CO and the danger from such concentrations to health and life in a small closed garage. Winkelmann[30] pointed out that toxic concentrations may persist for some time after the motor has been stopped.

In *public garages* the contamination of the air with CO seldom assumes such proportions as observed in private garages; nevertheless, sufficiently high concentrations may be encountered to cause subacute toxic effects especially with prolonged exposure. Salls[31] who studied the contamination with CO in public garages and repair shops found an average concentration of 0.009 per cent. In repair shops he found an average concentration of 0.011 per cent; in small repair shops where only incidental repairs were made 0.006 per cent; in commercial garages storing more than 5 cars 0.009 per cent; in [illegible]7 out of 71 workrooms in automobile repair shops more than 0.01 per cent with an average of 0.015 per cent and in [illegible] workrooms concentrations as high as 0.032 and 0.038 per cent. Bloomfield and Isbell[3] found an average of 0.0[illegible]1 per cent in the course of 102 tests made in [illegible]7 garages in 14 cities. Fifty nine per cent of these samples contained concentrations above 0.01 per cent and 18 per cent contained more than 0.04 per cent

Froboese[33] determined concentrations of 0.002 to 0.017 per cent in big automobile garages but most of them were below 0.01 per cent. These values are all considerably lower than those reported by Campolini[34] who found concentrations of 0.00–0.05 and 0.10 per cent 7 times in 31 commercial garages, 0.15 per cent 9 times and 0.20 per cent once. It appears therefore that the air in public garages may become contaminated to such an extent that continued exposure to such concentrations may be detrimental to health. In order to avoid this, certain precautions regarding ventilation and the running of motors within such structures must be taken.

Fatal accidents from the inhalation of CO from exhaust gases in garages have been reported repeatedly, as by Zangger[35] who also pointed out the medico-legal complications which may result from an incorrect diagnosis. Schmidt-Lamberg[36] stated that of 242 fatal accidents in garages reported in Prussia 85 per cent were caused by CO poisoning and he also stated that the number of such casualties is increasing. This is also indicated by a report of Hayhurst[37] on fatalities from CO poisoning during the winter periods of 1932-3, 1933-4 and 1934-5 in which the number of fatalities from this source were 5, 7 and 20 respectively.

In view of the great toxicity of the exhaust gases from automobiles the pollution of air and its possible toxic effects on the population have been investigated repeatedly. Table II contains a summary of the analytical findings of different investigators in this country and abroad and it shows that even in crowded traffic the concentrations are below the level considered to be dangerous even with continued exposure. On the other hand it appears possible that in heavy traffic guards and policemen may have sufficient exposure to cause moderate subjective and objective symptoms as will be shown later on. The reason for these low concentrations is that the exhaust gases are diluted very rapidly as shown by Keeser, Froboese, Turnau, Gross, Ritter, Kuss and Wilke.

The pollution of the air of *vehicular tunnels* with CO offers very considerable danger unless the concentrations are kept down to permissible levels by proper traffic regulations and adequate ventilation.

In this connection it should be pointed out that in some countries in recent years the danger of CO poisoning from exhaust gases has been considerably increased by the introduction of "producer gas" as motor fuel as illustrated by the reports of Radmark[44], Duvoir and Truffert[45], Barthe, Paris and Delsol[46], Noro[47], Feil[48] and Lumio[49].

The development of *aviation* has also created hazards from exhaust

gases to which pilots and passengers may be exposed As pointed out by White this hazard depends upon the type of exhaust leads fuselage etc and the gas may be carried back to the cockpit in sufficient amounts to produce concentrations up to 15 per cent CO hemoglobin in the blood of pilots and passengers Beyne and Goett[51] believed that there generally is little danger from this source, although certain types of airplanes with closed cabins may contain appreciable amounts of CO in the air of the carrier A more detailed discussion of this question was presented by Speert, and Bell[53] reported a case of subacute CO poisoning in a pilot

TABLE II

CONCENTRATIONS OF CO IN CITY STREETS

	Per cent CO	
	0.001-0.006 (average 0.0034)	Henderson and Haggard[18]
	0.005-0.026 (average 0.012)	Henderson and Haggard[18]
	0.00 -0.046 (average 0.0128)	Henderson and Haggard[18]
New York	0.002-0.031 (average 0.014?)	Henderson and Haggard[18]
	0.002-0.0 9 (average 0.0131)	Henderson and Haggard[38]
	0.007-0.015	Henderson and Haggard[38]
Paris	0.001-0.0044	Florentin 38(a)
United States	0.008 (only 24 percent of 141 samples had more than 0.01 percent)	Bloomfield and Isbell[37]
Paris	0.004-0.005	Cambier and Marcy[39]
	0.005-0.006	Cambier and Marcy[39]
	0.000-0.006	Keeser Froboese
Berlin	0.013-0.027 (exceptionally)	Turnau Gross Ritter Kuss and Wilke[40]
	0.015	Froboese[33]
	0.000-0.023	Boedicker[41]
Dresden	0.0004-0.004	Supfle Hofmann and May[42]
Budapest	0.0001-0.00	Winkler[43]

Berwald[54] reported that the concentrations of CO in the cockpits of 16 different types of Army airplanes ranged from 0.00.5 to 0.0 per cent but as found by Grow (quoted from Berwald[54]) with exhaust collector rings the concentrations may be reduced to 0.001 to 0.004 per cent That such concentrations may be exceeded considerably especially under unfavorable conditions, may be seen by a report by Beyne and Goett[51] who found in a certain type of plane with a closed cabin concentrations as high as 0.07 per cent when in slow flight

As already pointed out CO hazards may be encountered in the *steel industry* According to Watkins[5] dangerous concentrations may exist especially near the blast furnaces close to the runway while casting at the scrubbers and at the dust catchers while lower but still toxic concentrations may be found around the engines above the cupolas at open hearth furnaces foundries and mold shops and near the gas producers According to Hamilton[6] the danger spots in a steel plant when arranged according to the number of accidental CO poisonings were as follows mains 34 blast furnace tops 17 gas outside boilers 16 holders and washers 12 boiler pipes 6 blast furnaces 4 cleaning boilers 4 down comers 3 and furnace stacks 1 Burke[57] studied the pollution of the air in foundries during the pouring of ferrous and non ferrous metals and found that the production of CO could be traced to the use of pitch (powdered coal tar residue) in dry sand molding to sea coal (a finely powdered soft coal) used as a facing and to organic

TABLE III

INCIDENCE OF FATAL AND NONFATAL CO POISONINGS IN A STEEL PLANT DURING THE YEARS 1916 TO 1920 (HAMILTON 56)

Year	*Average number of men employed*	*Total number of CO poisonings*	*Total number of deaths*
1916	8,694	33	
1917	10 553	54	7
1918	11 339	57	2
1919	9,618	66	2
1920	10 825	1	
Total	51,019	211	13

core binding materials such as linseed oil and cornstarch Rossiter[8] pointed out that foggy weather may increase the potential danger from CO in that it may interfere with the dissipation of the gas Porous materials such as bricks may also absorb great amounts of CO especially if the gas is under pressure and this may be given off later and cause toxic effects The incidence of CO poisoning in the steel industry may be illustrated by Table III as published by Hamilton[56] It shows that fatal accidents are comparatively few This was also indicated by the report of Engel[59] who observed no fatalities or any complications in a group of 1 00 cases of CO poisoning in a steel plant and by the report of Rossiter[8] who saw only a few serious after effects in a group of 2 000 cases

Concentrations of CO which may be encountered in the steel industry, resulting from the blast furnace gas which may contain from 25 to 30 per cent CO (Willcox[61] and Engel) and from the generator gas which may have an equal percentage as illustrated in Table IV

Another potential source of CO poisoning in the metal industry is *welding* with which there may also be danger from exposure to metal oxides The danger is especially imminent when the welding is done in small enclosures such as tanks and pipe lines and it appears that the use

TABLE IV

CONCENTRATIONS OF CO IN VARIOUS OPERATIONS OF THE STEEL INDUSTRY

Location	*Concentration of CO in volume per cent*	*Author*
Blast furnaces		
Close to runway while casting	0.1 (0.2 and 0.[illegible] as extremes)	Watkins
On top	0.055-0.18 and more	Koelsch[18]
Scrubber	0.94	Watkins
Dust catcher	0.03	Watkins
Surroundings of gas engine	0.03 (0.01 and 3.4 as extremes)	Watkins
Above cupola of open hearth furnace	0.05 (0.0[illegible] and 0.1 as extremes)	Watkins
Around generator	0.12 (0.03 and 0.61 as extremes)	Watkins
Around generator	0.03	Koelsch[18]
Around generator (defective)	3.271 (0.117 and 10.4 as extremes)	Van Itallie and Steenhauer[61]
During charging	1.65	Koelsch[18]
During stoking	.62	Koelsch[18]
Foundries	0.05 (0.02 and 0.1 as extremes)	Watkins
Foundries	0.018 to 0.011	Koelsch[18]
Immediately after poring	0.01 (0.002 and 0.045 as extremes)	Burke
Molding	0.05 (0.02 and 1.0 as extremes)	Watkins

of the acetylene torch is more dangerous in this respect than electric arc welding

Dudding Dudley and Frederick[6] pointed out that confined spaces in ships (bulges and blisters) may contain small quantities of CO produced by the oxidation of boiled linseed oil used in paint and that these in combination with the reduced concentration of O on account of the same oxidation process and the corresponding increase of CO content may be potentially dangerous

The CO hazards in *mines* usually resulting from mine fires are too well known to need detailed discussion and victims of CO poisoning

are found in many mine disasters Such gases may travel long distances and may accumulate in distant sections of the mine

Closely related to the CO danger from underground mine fires are subterranean fires in piles of cinders or coal which may not be recognized easily and the combustion gases of which occasionally may travel considerable distances before reaching the surface

The vapors resulting from the use of *explosives*, especially in mines may carry considerable quantities of CO This is most likely to occur if the detonation is not complete and the shot burns out instead of exploding Even the relatively fresh air of dugouts trenches artillery emplacements and artillery turrets of battleships especially during rapid firing may contain sufficiently high concentrations of CO to cause serious and even fatal CO poisoning Because of the rapid diffusion of CO in the air fatal accidents are comparatively rare in the open field although tremendous quantities of CO may be generated One kilogram of modern high explosive is said to produce 600 to 800 liters of CO Fatal CO poisoning may occur however if the elimination of the gas from the organism is impaired by restriction of the respiratory movements if the victim is partially buried or because pulmonary edema may develop due to exposure to irritant gases such as nitric oxides as pointed out by Oettel[53]

Less frequent causes of CO poisoning are *accidents* where CO had been absorbed by dust and was gradually liberated in a small enclosure Toxic concentrations of CO may be produced by inadequately heated and improperly ventilated heating presses and from charcoal and gas heated flatirons One source of CO poisoning which has been reported *on only a few occasions is the contamination of the air by CO in safety* and divers helmets due to defects in the compressor or to contamination of the air filters with combustible materials Not only the air supplied for the protection of man but also anesthetic gases used medicinally may contain dangerous concentrations of CO

Absorption Fate and Excretion of CO

The *absorption* of CO takes place through the lungs and the amount absorbed varies at least to a certain extent with the respiratory activity and is affected therefore by certain factors such as the amount of physical exercise the concentration of CO in the air the humidity and by a deficiency of O The absorption of CO through the skin is possible but this is so small that it is without importance for any practical

purpose As shown in animal experiments CO may be absorbed through the mucous membranes of the body cavities such as the abdominal cavity and from subcutaneous tissues Although the former has no practical importance at all the latter may play a minor role in those cases where explosives burn within wounds The absorption of CO by the organism is controlled by various factors some of which are not well understood If, for instance as pointed out by Henderson and Haggard[61], 2 individuals of different size are exposed to the same concentration of CO, the smaller and younger one will absorb CO more rapidly on account of the more active metabolism The replacement of O in oxyhemoglobin by CO is determined by the ratio of respiratory volume to the size of the body and the amount of blood The respiratory volume of a person at rest bears a direct relationship to the surface of the body and the amount of blood has a direct relationship to the weight of the body It is a rule that the relative size of the surface increases with the inverse ratio of the mass This fact may therefore indicate that asthenic persons are more sensitive to CO than stout persons because their respiratory volume is comparatively greater than the amount of blood

Forbes Sargent and Roughton[65] showed that with exposure to 0 01 to 0 02 per cent CO in air the initial rate of uptake is proportional to the partial pressure of CO and that it increases with the ventilation rate though at a slower rate than the latter It is independent of the oxygen pressure and barometric pressure when these are below their normal values at sea level provided that allowance is made for the increase in ventilation rate because of hypoxia In contrast at high oxygen pressures the CO uptake is considerably reduced They noted considerable individual variations in the rate of oxygen uptake and assumed that a slow CO uptake probably is related to a low ratio of tidal air to the dead space in the lungs and/or to a low diffusion constant Goldman[6] showed that the rate of uptake of CO by the organism is linear with time until about one third of the equilibrium value of CO hemoglobin in blood is reached

In recent years much attention has been paid to the uptake of CO under reduced atmospheric pressure as encountered in airplanes Heim[66] developed on the basis of formulas worked out by Haldane Hill and Barcroft and Peters and Van Slyke a number of curves illustrating the variations in oxygen saturation at various altitudes for various concentrations of CO which show that the presence of CO in the atmospheric air lowers tolerance for high altitudes Lilienthal Riley Proemmel and

Franke[68] studied this question experimentally in 3 subjects while in equilibrium with inhaled gas air mixtures containing 0.005 to 0.015 per cent CO. They found that the distribution of CO hemoglobin, oxyhemoglobin and reduced hemoglobin and their related gas tensions follow the laws established by Haldane in vitro. Similar studies were reported by Lilienthal and Pine[69] who found that the rate of uptake of CO is inversely proportional to the partial pressure of oxygen, whereas the total barometric pressure plays a discernible role, and the effects of minimal anoxia due to altitude are additive to the effects of small amounts of circulating CO hemoglobin in producing moderately severe symptoms of anoxia. Halperin, Niven and McFarland[70] showed that a given percentage of CO hemoglobin in the blood at sea level produces approximately an equal effect as that of an equal decrease in oxyhemoglobin due to hypoxic anoxia, and that at simulated altitude a given percentage of CO hemoglobin produces an impairment equivalent to a further ascent which would cause an equal additional decrease in per cent oxyhemoglobin.

The *excretion* of CO takes place exclusively through the lungs by the reverse of the process responsible for its absorption and depends upon the rate and depth of the respiration. As pointed out by Haldane[71] the disappearance of CO from the blood always is slower than the absorption. The excretion is enhanced by physical exercise as shown by Sayers and Yant[72]. Sayers, Yant, Levy and Fulton[73] found that the rate of elimination from the blood varies directly with the initial saturation and decreases as the concentration in the blood is reduced. Thus it required one half hour to reduce the initial saturation of 35 per cent to 30 per cent, 1 hour more to lower it to 25 per cent, an additional 1½ hours to bring it down to 20 per cent, nearly 2 hours more to reduce it to 15 per cent, and an additional 3 to 5 hours or more to lower it to 5 per cent if air was inhaled. May[74] claimed that the intensity of the exposure to CO can be estimated from the saturation curve of the blood by determining the CO hemoglobin content of the blood at a given time. Sayers and Yant[72] found that the inhalation of pure O_2 caused elimination of CO about 4 times as fast as when normal air was inhaled by persons who had been gassed until their blood had been saturated with CO to the extent of 35 to 40 per cent CO hemoglobin. Under the same conditions inhalation of O_2 mixed with 8 and 10 per cent CO_2 caused excretion 5 to 6 times as fast as observed with inhalation of air. Similar favorable results were reported by Barac and Dor[75]. These studies, which are of fundamental importance for the treatment

purpose As shown in animal experiments CO may be absorbed through the mucous membranes of the body cavities, such as the abdominal cavity, and from subcutaneous tissues Although the former has no practical importance at all the latter may play a minor role in those cases where explosives burn within wounds The absorption of CO by the organism is controlled by various factors some of which are not well understood If, for instance as pointed out by Henderson and Haggard[61], 2 individuals of different size are exposed to the same concentration of CO the smaller and younger one will absorb CO more rapidly on account of the more active metabolism The replacement of O in oxyhemoglobin by CO is determined by the ratio of respiratory volume to the size of the body and the amount of blood The respiratory volume of a person at rest bears a direct relationship to the surface of the body, and the amount of blood has a direct relationship to the weight of the body It is a rule that the relative size of the surface increases with the inverse ratio of the mass This fact may therefore indicate that asthenic persons are more sensitive to CO than stout persons because their respiratory volume is comparatively greater than the amount of blood

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Roughton Root and Gregersen[3] found that less than 0 1 per cent if any of radioactive CO was oxidized to carbon dioxide

Combination of CO With Blood Pigments and Similar Compounds

Combination With Hemoglobin

The toxic action of CO is predominantly based on its affinity to hemoglobin resulting in the formation of CO hemoglobin and the subsequent interference of this combination with the oxygen supply of the body Hemoglobin binds equal quantities of O and CO

As found by Hufner[31] and later confirmed by Haldane[8] Nicloux and others the combination of hemoglobin with CO and O when in contact with a mixture of the two gases follows the law of mass action It was pointed out by Haldane[5] that the toxic action of CO or its affinity to hemoglobin diminishes as the O tension increases Hoppe Seyler[37] assumed that in this reaction 1 atom of iron in the hemoglobin reacts with 1 molecule of CO This was confirmed by Hufner and Kuster[38] But Zeile and Gnant who studied spectrophotometrically the hemochromogenes of proto and meso hemochromogen of the cyto chrome system found that 4 heme combine with 1 globin to form hemochromogen and that additional heme may form less stable compounds with less affinity These and similar studies on the structure of hemoglobin were discussed by Drabkin[6] CO hemoglobin has a molecular weight of approximately 68 000 and may be obtained in pure crystallized form the crystals being isomorphous with those of oxy *hemoglobin It is less soluble than the latter and more resistant to* oxidation

As shown by Haldane and Lorrain Smith[91] CO hemoglobin is decomposed by potassium ferricyanide with liberation of CO and simultaneous oxidation to methemoglobin but according to Muller this decomposition is slower than in the case of oxyhemoglobin

From the work of Haldane and others it appears that the affinity of hemoglobin to CO is about 300 times greater than its affinity to O Recently Lilienthal Riley Proemmel and Franke[81] determined this affinity constant for the hemoglobin of man as 204 ± 10 per cent According to Roughton the uptake and release of oxygen from the red blood cells is determined by the diffusion through their membrane the diffusion within their interior and the chemical reaction within their

of CO poisoning will be discussed in greater detail in a later section. It will be shown that the time necessary for complete elimination may vary considerably depending upon the condition of the patient, and it appears that, as stated by Breitenecker[76, 77], with an initial concentration of 50 per cent CO hemoglobin in the blood elimination should be complete at the end of 17 hours if the patient breathes normally and remains conscious. Breitenecker[76, 77] pointed out that the maintenance of a certain concentration of CO hemoglobin in the blood over a longer period of time appears to be more detrimental, especially for the central nervous system, than higher concentrations for shorter periods. In contrast to Breitenecker, Larmer and Crittenden[78] found from 6 to 7 per cent CO hemoglobin in the blood of steel mill workers at the end of the shift, and when returning to work after a 16 hour rest period per cent CO hemoglobin was still present. If the respiratory exchange is impaired for some reasons, CO may be detectable in the blood after longer periods of time. Kohn-Abrest[8], Duvoir, Truffert and Derobert[9] and Duvoir, Derobert and Truffert[1] claimed that in subacute CO poisoning CO hemoglobin may be present in the blood for a long period of time.

Concerning *the fate of CO in the organism*, it has been established that this is not oxidized in the body. In a study of the excretion of CO Roughton and Root[8] found that in normal men, when breathing oxygen or air, the amount of CO found in the expired air was only 60 to 70 per cent from that currently lost from the blood during the first hour after the administration of CO, but that with continued inhalation of oxygen for four hours 96 per cent of the initially absorbed CO could be recovered. They assumed that 30 to 40 per cent of the CO fraction lost from the blood during the first hour and unaccounted for in the expired air must have combined reversibly with some hemoglobin-like pigments outside the main blood stream. This assumption was supported by the findings of Tobias, Lawrence, Roughton, Root and Gregersen[83] who studied the distribution of relatively large doses of radioactive CO in man and who found by Geiger counter measurements that the liver retained an exceptionally high and prolonged phase of radio-activity which either can be explained by an engorgement of this organ with radioactive CO hemoglobin or by the presence of a pigment in this organ which possesses a higher affinity to CO than hemoglobin. Roughton and Root[8] found no evidence that in moderate CO poisoning significant amounts of CO are eliminated through the skin, the sweat, urine or feces, and that no measurable amounts of CO are lost by oxidation or other forms of metabolism, and similarly Tobias, Lawrence

each concentration an equilibrium is reached which is not exceeded as illustrated by Fig - which was published by Hanne and quoted by Kalthoff[1 7] As shown by Sayers Meriwether and Yant[103] the combination of CO with hemoglobin takes place slowly when the subject is exposed to low concentrations and remains at rest and that under such conditions many hours are required to reach an equilibrium Similarly Haldane and Lorrain Smith[9] stated that with higher concentrations

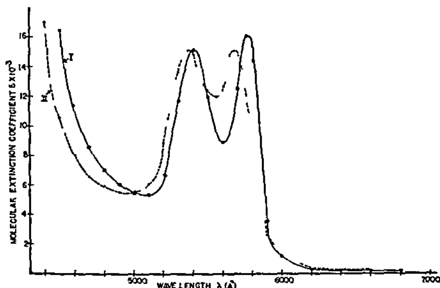


Fig 1 Absorption spectra of CO hemoglobin and oxyhemoglobin in the visible region (Horecker 1943) Curves I and II represent absorption constants obtained from pure calf hemoglobin for oxyhemoglobin and CO hemoglobin respectively o and • represent constants for oxyhemoglobin and CO hemoglobin respectively of human blood

the saturation point is reached much more rapidly so that toxic effects may become manifest instantaneously

The dissociation of CO hemoglobin progresses in the form of a rectangular hyperbola as was shown by Douglas and Haldane[1 4] the percentage saturation with a given concentration of CO varying however with different individuals and species

As pointed out by Haldane[105] it would be difficult to understand some of the symptoms of CO poisoning if the action of CO were simply to diminish the O -carrying power of the blood without modifying

interior which studies were amplified in a later paper[93] He found[91, 92, 93] that the reaction between oxygen and hemoglobin is about 10 times as fast as the reaction between CO and hemoglobin and that the greater stability of CO hemoglobin must be due to the extremely low velocity constant of its dissociation which he determined as 0 004

The most important physico chemical characteristic of CO hemoglobin is its absorption spectrum In a dilution which still allows the recognition of the green part of the spectrum it shows absorption bands between Frauenhofer's lines D and E which are nearly identical with those of oxyhemoglobin but which unlike the latter persist after the addition of a reducing agent such as ammonium sulfide or Stokes solution The wavelength of the maximum of the narrower absorption band (A band) of oxyhemoglobin usually is given as 5 770 Å and that of the wider (B band) as 5 430 Å More recently Drabkin and Austin[7] found the values to be 5 750 and 5 400 Sidwell Munch Barron and Hogness[9] found them to be 5 760 and 5 415 and Horecker[95] found them to be 5 765 and 5,400 In comparison to these the absorption bands of CO hemoglobin are shifted toward the violet side of the spectrum and the wavelength of their maxima is usually given as 5 700 Å and 5 360 Å respectively Drabkin and Austin[7] gave them as 5 690 and 5,390 and Horecker[98] gave them as 5 680 and 5 375

Fig 1 illustrates the absorption spectra of oxy- and CO hemoglobin in the visible region as given by Horecker[98] It illustrates the shift of the absorption bands of CO hemoglobin toward the violet as compared with those of oxyhemoglobin As shown by Horecker[94] in contrast to oxyhemoglobin CO hemoglobin shows practically no absorption in the infra red region

Although the combination of CO with hemoglobin is more stable than that of O the process of the formation of CO hemoglobin is reversible especially if the percentage of the O in the inhaled air is increased On the other hand it is quite resistant towards decomposition by putrefaction

Haldane and Lorrain Smith[99] and Haldane[100] observed that it is decomposed by light Hartridge[101] showed that dilution lactic acid and CO certain other acids and basic salts have no influence on the final saturation of hemoglobin with CO but that light has a very definite influence on its stability as shown by Hasselbalch[10] and that this dissociation is not bound to the presence of oxygen

The speed and the degree of the combination of hemoglobin with CO depends largely upon the concentration of the latter, and that for

hemoglobin and both have the same amount of oxyhemoglobin they are nevertheless quite differently equipped to meet the O demand of the tissues Whereas the oxyhemoglobin of B dissociates along the normal curve as illustrated by line 1 the oxyhemoglobin of A dissociates along the curve of line 4 If the O tension in the blood of each is 13

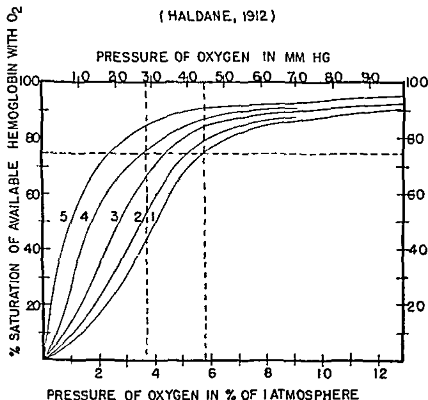


Fig 3 Dissociation of oxyhemoglobin in the presence of various quantities of CO hemoglobin

1 = 0 per cent
2 = 10 per cent
3 = 5 p r cent
4 = 50 per cent
5 = 75 per cent

the properties of the remaining hemoglobin Haldane[106] showed that as the saturation of blood with CO increases the dissociation of the remaining oxyhemoglobin decreases, as illustrated in Fig 3 This was

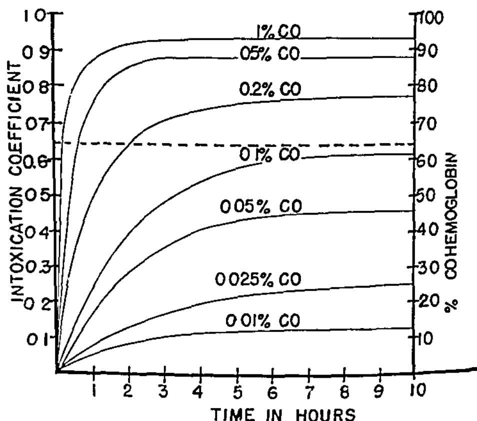


Fig Shows speed of saturation of hemoglobin with different concentrations of CO until equilibrium between the concentration of CO in air and in blood is produced (redrawn from Hanne 1935)

confirmed later by Stadie and Martin[106] Therefore if the blood of a person A is saturated to the extent of 50 per cent and another person B is anemic to the extent that his blood carries only 50 per cent oxy

relation between carbhemoglobin content and degree of the reduction of hemoglobin If therefore the reduction of oxyhemoglobin to hemoglobin is diminished as for example by the formation of CO hemoglobin less base will be available to neutralize CO_2 and this will result in acidosis It appears therefore that CO interferes not only with the O carrying capacity of the blood but also with its ability to promote the transportation and dissociation of CO Whether or not this inter-

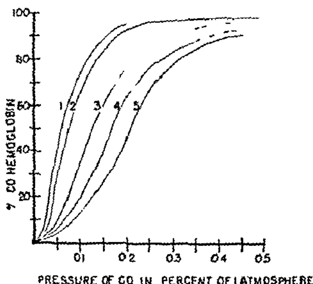


Fig 4 Dissociation of CO hemoglobin under different pressures of CO_2 Curves 1 and 2 give the dissociation in the presence of O mm Hg CO and 3 4 and 5 in the presence of 19 42 and 9 mm Hg respectively

ference with the removal of CO from the tissues plays a separate detrimental role in the mechanism of CO poisoning appears to be open to discussion because it seems quite possible that an accumulation of CO in the tissues may favor the release of the available O from oxyhemoglobin and thus antagonize he inhibiting effect of CO hemoglobin on the dissociation of oxyhemoglobin

per cent of an atmosphere or 99 mm Hg A's blood is about 1 per cent more saturated than B's the saturation of the available hemoglobin with O_2 being 93 and 92 per cent, respectively If however the saturation of the venous blood of both persons with O_2 is reduced to 75 per cent, the blood in A's veins will be under an O_2 tension of only 3 5 per cent or 26 6 mm Hg while that in B's will be 5 8 per cent of an atmosphere or 44 1 mm Hg This illustrates why B will behave quite normally, whereas A may show serious symptoms of O_2 deficiency under conditions which are comparable as far as O_2 consummption and rate of saturation are concerned and it explains why a 50 per cent saturation of the blood with CO is a serious condition This figure also illustrates the fallacy of an indiscriminate comparison of the phenomena of CO poisoning with those produced by anoxemia due to other causes

The effect of inhalation of CO_2 on the elimination of CO from the organism which will be discussed under treatment of CO poisoning has been explained usually by its stimulating effect on the respiratory center resulting in a more complete and more rapid ventilation of the lungs Stadie and Martin[105] pointed out that this may not be the only or most important mechanism of action but that the increased hydrogen ion concenration of the blood during the inhalation of CO_2 must be considered also By theoretical considerations supported by experimental evidence they came to the conclusion that any increase of the acidity of the blood would result in an increase of the dissociation and elimination of CO from the blood if other conditions remained unchanged

Similarly Douglas Haldane and Haldane[106] had shown that the dissociation of CO hemoglobin is facilitated by the presence of CO_2 as illustrated by the curves given in Fig 4

In addition to its function as carrier of oxygen to the tissues hemoglobin is also involved in the liberation of carbon dioxide inasmuch as it was shown by Henriques[107] that it enormously increases the rate at which the system $CO_2 \rightleftharpoons NaHCO_3$ in which carbon dioxide exists in the blood loses CO_2 to a vacuum In the opinion of Van Slyke and Hawkins and of Stadie and O Brian (both quoted from Mirsky and Anson[108]) this is mainly due to a catalytic action of hemoglobin Other investigators such as Bohr Henriques Magaria and Green and Meldrum and Roughton (quoted from Anson and Mirsky[108]) believed that the carbon dioxide of the blood is partly bound to hemoglobin as carbhemoglobin, and according to Lemberg[109] 30 per cent of the CO_2 transported by the arterial blood and 75 per cent of that transported by the erythrocytes is in the form of carbhemoglobin and there exists a linear

cently Blomer and Kiese[11] could not confirm in dogs the statement of Barkan that following CO poisoning the reduction of the easily split table iron persists for some time. It should however be pointed out that the observations of Tobias, Lawrence, Roughton, Root and Gregersen[83] who noted an unexpectedly high and prolonged radioactivity in the liver after inhalation of radioactive CO also may be interpreted as indication of greater affinity of CO to certain bile pigments than to hemoglobin.

Combination with Other Pigments and Enzymes

Like hemoglobin, myoglobin enters a combination with CO, but as shown by Theorell[1,4] the ratio of the partial pressure of oxygen and CO for the same quantities of myoglobin and hemoglobin is of an entirely different order and according to Millikan[1,4] CO myoglobin dissociates more readily than the corresponding hemoglobin compound.

As with CO myoglobin the combination CO with hemochromogen, cytochrome, hemitin, Warburg's respiratory ferment and catalase are rather unstable and hardly of physiological importance as illustrated by the review of von Oettingen[4].

Detection and Determination of CO Hemoglobin in the Blood

In view of the very variable clinical picture of CO poisoning it is of paramount importance that the presence of CO hemoglobin in the blood be established by qualitative tests and preferably also by quantitative determinations. They have been discussed extensively by von Oettingen[4] and for this reason only a few of these will be mentioned in the following.

Of all *qualitative tests for the detection of CO* the following appear to be most suitable:

Landois' test[1]. Three c.c. of blood containing CO hemoglobin are diluted to 100 c.c. with distilled water mixed with a few drops of potassium hydroxide solution and a small amount of an aqueous solution of pyrogallic acid. After shaking it remains red, whereas normal blood assumes a dirty red color.

Test of Kunkel[1,6] *and Welzel*[1,7]. When 10 c.c. of undiluted blood containing CO hemoglobin are mixed with 15 c.c. of a 20 per cent solution of potassium ferricyanide and c.c. of 40 per cent acetic acid and

Combination With Pseudohemoglobin

Barkan[110] showed that by treating blood solutions with diluted acid part of the iron (easily splittable iron) can be liberated separated by ultra-filtration and determined in the ultra filtrate in ionic form He believed that this iron is derived from a pigment pseudohemoglobin which according to Barkan and Schales[111], is an intermediate between hemoglobin and bilirubin in that the heme ring system is open at one point thus approaching the constitution of bilirubin as established by Fischer and his school It differs however from bilirubin in that it still contains iron bound to the nitrogen atoms of the 4 pyrrole rings It resembles the green hemin of Warburg and Negelein[112] as determined by Lemberg[113] in that this also splits off iron readily under the influence of dilute hydrochloric acid but in opposition to pseudohemoglobin the green hemin is a hemochromogen and therefore lacks the protein carriage and is not affected by CO Pseudohemoglobin is a regular constituent of normal blood and forms from 5 to 10 per cent of the total hemoglobin according to Winegarden and Borsook[114] 4 to 6 per cent Its function is not known, and the question of whether it represents only a decomposition product of hemoglobin being an intermediate between this pigment and bilirubin or whether it has to perform physiological functions in the organism has not been answered

Barkan and Berger[115] and Barkan and Schales[116] showed that in CO poisoning the amount of "easily splittable iron is greatly reduced Similar results were reported by Schwarz and Deckert[117] who found in the majority of cases of CO poisoning studied in this respect an unmistakable reduction of the easily splittable iron and they found that the values return to normal after from 4 to 8 days Similarly Beckmann[118] showed that in acute CO poisoning the reduction of the 'easily splittable iron outlasts considerably the detectable presence of CO hemoglobin and he believed that this phenomenon is also well suited to the detection of subacute CO poisoning However Schwarz and Deckert[117] were unable to establish a definite relation between the degree of this reduction and the severity of the exposure This question was studied experimentally by Reploh and Bredemann[119] in guinea pigs Whereas normal animals showed variations of the 'easily splittable iron between 17 and 18 mgm per liter of blood in acutely poisoned guinea pigs this was 13 5 mgm after 10 minutes 1 3 mgm after 15 minutes and 12 9 mgm after 20 minutes After 4 days there was a gradual return to normal values which were reached after a period of 8 to 10 days Similar results were reported by Rooks[120] More re

tion V is the loss of CO to be calculated a is the percental concentration of CO as determined in such samples B is the blood volume and L is the air volume above the blood in the container

The methods for the quantitative determination of CO hemoglobin in blood may be classified into colorimetric methods optical methods and methods based on the liberation of CO with its subsequent determination by some other means

Sayers Yant and Jones[33] and Sayers and Yant[135] worked out a method which allows rapid and accurate determinations of the CO hemoglobin This method is said to have the advantages of giving accurate results in the field and in the laboratory and of being compact and portable and simple enough to give reliable results even in the hands of a person without special training In this procedure 0 1 c c of blood is diluted to 2 c c with distilled water care being taken to wash out the adhering blood from the pipette by sucking water several times back and forth To prevent clotting this should be done as rapidly as possible Immediately following this 0 04 gm tannic pyrogallic acid (in solid form or in solution) is added and thorough mixing is insured by shaking the mixture This is then kept at room temperature for 15 minutes and compared with standards which are made either by diluting CO saturated and defibrinated blood in certain proportions and treating these in the same way or by using artificial standards made up with artist s pigments

The *spectrophotometric methods* generally give more exact results than the spectroscopic methods The spectrophotometric measurements are based on the fact that the extinction coefficients of colored solutions for a certain wave length are directly proportional to the concentration If ε and ε_1 are the extinction coefficients and C and C_1 the corresponding solutions this relation is illustrated by the formula $C\ \varepsilon = C_1\ \varepsilon_1$

The molecular extinction coefficient ε is defined by the equation

$$\varepsilon = \frac{c \times 1}{\log \frac{I_0}{I}}$$

where c is the concentration in moles per liter 1 the cell length in cm Io the incident light intensity and I the transmitted light Such determinations are greatly facilitated by tables as worked out by Hufner and others which allow the calculation of the absolute quantity of each component as for instance oxyhemoglobin and CO hemoglobin

shaken, the mixture turns bright red whereas with normal blood it assumes a gray color According to Fishbein[illegible] this, among the more common tests is the most reliable in case the blood is contaminated with formaldehyde as after embalming

Hoppe Seyler's spectroscopic test[129] As mentioned before both oxyhemoglobin and CO hemoglobin have two absorption bands between the D and E lines Upon the addition of ammonium sulfide or Stokes solution ([illegible] per cent ferrous sulfate plus 3 per cent tartaric acid in water) these bands persist in the case of the CO hemoglobin whereas in oxyhemoglobin a single broad band is formed The sensitivity of this test often appears to be overestimated and it seems to be sensitive only to concentrations down to 15 to 20 per cent of CO hemoglobin

Both for the clinical evaluation and for forensic poisonings the *quantitative* determination of CO hemoglobin is of great importance and this subject has been reviewed by von Oettingen[4]

Before entering upon a discussion of the different methods, it may be advisable to mention in a few words the precautions to be observed in obtaining mailing and storing blood samples prior to the determination of CO hemoglobin Sayers O Brien Jones and Yant[130] developed a modification of the Keidel tube for collecting and shipping CO blood using 0 3 per cent sodium fluoride as anticoagulant This was found to be superior to 0 [illegible] per cent sodium oxalate which caused darkening of the blood upon standing They showed that under these conditions the CO content of the blood was not affected As pointed out by Hodyo and Wehrli[131] CO hemoglobin blood may be kept for a long time in well stoppered and well filled containers but direct contact with air especially if it is replaced from time to time by opening the bottle may cause loss of CO In determining CO hemoglobin in the blood of cadavers it should be kept in mind that CO blood does not coagulate very readily For this reason sedimentation of the red blood cells may take place within the cadaver and thus it is possible to collect blood samples containing either a disproportionate number of red blood cells or an abnormal amount of serum In order to avoid erroneous results it is necessary in such cases to divide the blood sample in two equal parts and determine in one of these the CO content and in the other the CO capacity after complete saturation with CO According to Wehrli[131] the loss of CO in blood specimens which were shipped in incompletely filled containers may be calculated according to formula $V = \frac{0\ 5L}{a \times B}$ In this equa

Slyke[139] Van Slyke and Neill[1] Van Slyke[141] and Sendroy and Liu[14] Van Slyke and Robscheit Robbins[143] determined the CO by absorption in Winkler's cuprous chloride solution Van Slyke Hiller Weisiger and Cruz[144] described a further improvement of the technique which allows the determination of CO hemoglobin total hemoglobin active hemoglobin and inactive hemoglobin

Scholander and Roughton[14] [145] worked out a micro determination which requires not more than 40 to 50 mm³ of blood The blood is mixed in 1 1 c c syringe with ferricyanide containing potassium bicarbonate and saponin An acid buffer then is added The CO thus liberated provides the gas phase for the extraction of other blood gases including CO CO and O are absorbed by alkaline pyrogallol solution and a small bubble containing the remaining CO and nitrogen is measured in a graduated capillary attached to the nozzle of the syringe The CO is then absorbed by Winkler s cuprous chloride ammonium chloride solution and the remaining gas is measured again The difference between these two readings gives the CO content of the blood with an accuracy of 0 2 volume per cent CO or 1 per cent CO hemoglobin This procedure was modified further by Roughton and Root[147]

Relation Between Concentration of CO Hemoglobin in the Blood and the Toxic Symptoms

As to the relation between the concentration of CO hemoglobin in *the blood and the toxic symptoms Table V gives a summary of the* findings of Sayers and Yant Shrader and Mitchell[11] and Killil[149] As pointed out by the latter the pulse rate increases with the CO hemoglobin content of the blood

As illustrated in Table V and as pointed out by Nicloux[1] and Balthazard and Melissinos[1 1] concentrations up to 20 per cent cause no serious toxic symptoms with single exposures On the other hand such concentration may cause mild toxic effects with continued exposure as illustrated by the report of Ciampolini[34] who found among 42 garage workers with a CO hemoglobin level of less than 20 per cent 42 complaints of headache 7 of nervous manifestations 6 of gastric complaints and in 24 men pallor of the skin Similarly Wilson Gates Owen and Dawson[1] reported that traffic policemen with concentrations of 20 to 30 per cent of CO hemoglobin complained about slight headache and quickened pulse rate According to Forbes Dill DeSilva and Van

Horecker and Brackett[134] developed a method for the determination of CO hemoglobin which is based on the spectrophotometric determination in the near infra-red region of the spectrum between 7 000 and 10 000 Å. The method is rapid and requires only a few manipulations and permits the determination of total hemoglobin, CO hemoglobin and methemoglobin in the same sample of blood. From each sample of blood are made 3 absorption measurements. From the first measurement in the infra-red a density (D) is obtained. After this the same sample is treated in the absorption cell with potassium cyanide to convert methemoglobin to cyanmethemoglobin, and the density ('D) is measured against the same wavelength interval. The sample is then diluted and a third determination (D_1) is made in the visible region. Results obtained with this method are said to compare favorably with those obtained with the Van Slyke apparatus, the accuracy being 1.5 per cent for CO hemoglobin. The important attribute of this method is that monochromatic light is not required, and the method can be applied with simple portable instruments as for instance the Coleman spectrophotometer where a dial setting of 4 965 and 8 000 Å was used.

In the determinations of CO hemoglobin which are *based on the liberation of CO* from the blood and subsequent determination of the gas by means of some of the analytical methods, procedures similar to those utilized for its determination in air have been used.

In order to secure correct data it is essential that the CO be completely *liberated from its* combination with hemoglobin. Haldane and Lorrain Smith[135] showed that by the addition of potassium ferricyanide both O_2 and CO may be liberated from their combination with hemoglobin. Modifications of this procedure were introduced by Van Slyke and Neill[136] and Martinek and Marti[137] who used a potassium ferricyanide solution of the following composition, potassium ferricyanide 8 gm C.P., lactic acid 40 c.c., saponin 3.0 gm, caprylic alcohol 3.0 c.c. and distilled water to make 1 000 c.c.

Von Fodor[138] liberated the CO at 90° to 95° C and removed it by means of a slow air current which passed through lead acetate and dilute sulfuric acid into a palladium chloride solution of 0. per cent and determined the amount of palladium reduced in this way.

Van Slyke and Salvesen[139] showed that CO hemoglobin could be determined in the Van Slyke apparatus by measuring, after the absorption of oxygen in alkaline pyrogallol solution, the liberated CO directly at atmospheric pressure, making correction for the nitrogen dissolved in the blood. The method was later extended by Harington and Van

TABLE V (Cont.)

RELATION BETWEEN TOXIC SYMPTOMS AND THE CONCENTRATION OF CO HEMOGLOBIN IN THE BLOOD

Sayers and Yant		[illegible] and Mitchell[14]		Kill[illegible][19]		
Per cent CO Hemoglobin	Symptom	Per cent CO Hemoglobin	Symptoms	Per cent CO Hemoglobin	Immediate Effects	Late Effects
40-50	Same as previous item with more possibility of collapse and syncope and increased respiration and pulse					
50-60	Syncope, increased respiration and pulse, coma with intermittent convulsions and Cheyne-Stokes respiration	60-80	Fainting and unconsciousness and death due to cardiac paralysis and cardiac failure			
60-70	Coma with intermittent convulsions, depressed heart action and respiration and possibly death					
70-80	Weak pulse, slow respiration, respiratory failure and death					

TABLE V

RELATION BETWEEN TOXIC SYMPTOMS AND THE CONCENTRATION OF CO HEMOGLOBIN IN THE BLOOD

Sayers and Yant[5]		Sl rader and Mitchell[148]		Killik[149]		
Per cent CO Hemo globin	*Symptoms*	*Per cent CO Hemo globin*	*Symptoms*	*Per cent CO Hemo globin*	*Immediate Effects*	*Late Effects*
0-10	No symptoms					
10-20	Tightness across forehead possibly slight headache and dilation of cutaneous blood vessels			Below 20	—	Negligible (7½ hours of exposure)
20-30	Headache and throbbing in temples	20-30	Frontal headache sometimes stiffness often nausea and feeling of fatigue these symptoms were accentuated by exercise	Below 30	Negligible	With 5½ to 7 hours of exposure severe headache lasting about 6 hours
				30-35	Throbbing and sensation of fullness in head slight headache and sometimes nausea	With 6 hours of exposure the same after effects as given above
30-40	Severe headache weakness stiffness dimness of vision nausea vomiting and collapse	30-50	Basal headache stiffness and general weakness	35-42	More definite headache drowsiness (sometimes extreme) faintness nausea and sometimes vomiting Symptoms more marked with physical exertion	With exposure for 6-7 hours very severe headache and nausea lasting 3 to 6 hours quite incapacitating for the rest of the evening

tims blood over the CO hemoglobin content found after complete saturation of such blood with CO is considered as suggested by Balthazard and Nicloux[1,8] Such data as published by Nicloux Gelma and Simonin[161] Simonin[168] and Kohn Abrest[16] are given in Table VII

TABLE VII

COEFFICIENT OF INTOXICATION AS DETERMINED IN THE BLOOD OF VICTIMS OF CO POISONING

Number of cases	Coefficient CO Hemoglobin / Total CO Hemoglobin	Author
1	[illegible]	Nicloux Gelma and Simonin[14]
1	0 89	Nicloux Gelma and Simonin[1]
1	0 88	Nicloux Gelma and Simonin[16]
1	0 87	Nicloux Gelma and Simonin[161]
1	0.85	Nicloux Gelma and Simonin[14]
1	0 80	Simonin[166]
1	0	Nicloux Gelma and Simonin[1]
39	more than 0.6	Kohn Abrest[16]
19	0 59-0 5	Kohn Abrest[1]
8	0.49-0.4	Kohn Abrest[16]
5	39-0 3	Kohn Abrest[16]
	0 29-0	Kohn Abrest[16]
3	0 19-0 1	Kohn Abrest
4	below 0 1	Kohn Abrest[1]

It is obvious that the concentrations found at death will not necessarily represent the maximal saturation because if the victim continues to breathe after removal to fresh air the original concentration may be *reduced considerably and such determinations represent only the actual* fatal concentration if the victim has been found dead in the toxic atmosphere As indicated by the findings of Kohn Abrest[16] and also as expressed by Nicoloux[1,0] the coefficient of intoxication usually will be found around 0 60 to 0 66 only exceptionally when death results *rapidly from high concentrations* will *it be between 0 7 and 0 9* it appears reasonable to assume that as stated by Balthazard and Melissinos[151] in cases where the coefficient is between 0.4 and 0 8 CO is the main if not the sole cause of death while with values below 0 05 death is very possibly due to some other cause than CO poisoning

Animal experiments reported by Fehling[15] *Dreser*[159] *and Ni*cloux[1,0,1,1,1] have shown that in pregnant animals exposed to CO the blood of the fetus contains CO hemoglobin Since the maternal blood

Deventer[1] normal persons are not affected with regard to their reaction time, binocular vision coordination of hand and eye until the CO hemoglobin level in their blood has reached 30 per cent or more and they felt subjectively well at this concentration and showed no abnormalities with regard to pulse rate respiration and blood sugar level It should however be pointed out that in this group the duration of the exposure was only 10 to 20 minutes which may explain this discrepancy from the findings previously mentioned

The blood of normal persons may contain small quantities of CO hemoglobin Hanson and Hastings[1] determined the CO hemoglobin content of non smokers who had no habitual exposure to automobile exhaust gases as 1 5 per cent Bland[1] found 0 9 and 1 0 per cent

TABLE VI

PER CENT CONCENTRATION OF CO HEMOGLOBIN IN THE BLOOD OF VICTIMS OF CO POISONING

Per cent CO Hemoglobin	*Author*
[illegible]	Balthazard and Nicloux[158]
80 and more	Shrader and Mitchell[11]
60 65 75 76 (occasionally 40 and 45)	Spilsbury[1]
4, 6	Martland[18]
28	Martland[1]
48 5	Hufnagel[101]
65 75	Oettel[1, 113]

Duvoir and Truffert[4] considered 2 per cent CO hemoglobin as normal values and Hanson and Hastings[1] reported normal values of 1 5 per cent In smokers the CO hemoglobin level is slightly higher than in nonsmokers Hanson and Hastings[1] found values of 3 1 to 4 3 per cent Schmidt[1, 157] up to 4 2 per cent and even 10 16 per cent when the smoke was inhaled

The question at which level of CO hemoglobin in the blood establishes a fatal concentration naturally has aroused much interest Whereas in animal experiments these values vary between 80 and 90 per cent as reported by different authors the findings in victims of CO poisonings show considerable variations as illustrated in Table VI Gettler and Freimuth[1] found that of 65 fatalities from CO poisoning 23 5 per cent showed less than 60 per cent and 9 per cent less than 50 per cent Similar variations are found if, instead of the actual value of CO hemoglobin the ratio of the amount of CO hemoglobin in the vic

tims blood over the CO hemoglobin content found after complete saturation of such blood with CO is considered as suggested by Balthazard and Nicloux[1 8] Such data as published by Nicloux Gelma and Simonin[16] Simonin[168] and Kohn Abrest[167] are given in Table VII

TABLE VII

Coefficient of Intoxication as Determined in the Blood of Victims of CO Poisoning

Number of cases	Coefficient CO Hemoglobin / Total CO Hemoglobin	Author
1	0.89	Nicloux Gelma and Simonin[16]
1	.89	Nicloux Gelma and Simonin[16]
1	0.88	Nicloux Gelma and Simonin[1]
1	0.8	Nicloux Gelma and Simonin[16]
1	0.85	Nicloux Gelma and Simonin[15]
1	0.80	Simonin[168]
1	0.7	Nicloux Gelma and Simonin[16]
39	more than 0.6	Kohn Abrest[16]
19	0.59-0.5	Kohn Abrest[16]
8	0.49-0.4	Kohn Abrest[15]
5	0.39-0.3	Kohn Abrest[1]
	0.29-0.2	Kohn Abrest[15]
3	0.19-0.1	Kohn Abrest[1]
4	below 0.1	Kohn Abrest[16]

It is obvious that the concentrations found at death will not necessarily represent the maximal saturation because if the victim continues to breathe after removal to fresh air, the original concentration may be reduced considerably and such determinations represent only the actual fatal concentration if the victim has been found dead in the toxic atmosphere As indicated by the findings of Kohn Abrest[1] and also as expressed by Nicoloux[1 0] the coefficient of intoxication usually will be found around 0.60 to 0.66 only exceptionally when death results rapidly from high concentrations will it be between 0.7 and 0.9 it appears reasonable to assume that as stated by Balthazard and Melissinos[1 1] in cases where the coefficient is between 0.4 and 0.8 CO is the main if not the sole cause of death while with values below 0.05 death is very possibly due to some other cause than CO poisoning

Animal experiments reported by Fehling[16] Dreser[169] and Nicloux[1 111 11] have shown that in pregnant animals exposed to CO the blood of the fetus contains CO hemoglobin Since the maternal blood

does not pass directly into the fetal circulation this is only possible if the CO hemoglobin is dissociated in the placenta and the free CO enters the fetal blood

Clinical Picture of Acute CO Poisoning

The clinical picture of CO poisoning shows considerable variations There is practically no organ which may not be affected by CO and for this reason the symptomatology of CO poisoning will be discussed with reference to various organs and organ functions

Circulatory Changes in CO Poisoning

In many cases of prolonged exposure to CO there is an *increase of the number of red blood cells* as reported by numerous observers (see von Oettingen[4]) This has been observed also in animal experiments Whereas according to some reports this hyperglobulemia is very considerable in most instances with moderate exposure the values are within normal limits as pointed out by Humperdinck[1 8] and in subacute poisonings a reduction of the number of red blood cells has been reported as by Beck and Fort[1??], Berger and Grill[173] and Arneth and Albacht[176] In rabbits Valchera[191] noted a primary increase and subsequent decrease of the number of red blood cells the latter being associated with reticulocytosis Brieger[177 178] noted in acute CO poisoning of dogs in most instances polycythemia usually it was a late effect fully developed only several days after the exposure and associated with signs of stimulation of the bone marrow With continued exposure to lower concentrations of CO which caused a CO hemoglobin level of around 20 per cent this caused a primary significant increase and later a decrease below normal values

The polycythemia may be paralleled by a similar *increase of hemoglobin* but this is not an absolute rule, and hyperglobulemia with low hemoglobin values may be observed occasionally

It appears that disturbances of the *white blood cell picture* are less common and less pronounced than those of the red blood cells nor are there reports on the appearance of *pathological blood cells* except occasional observations as by Karasek[179] on eosinophilia and myelocytosis Similarly the number of *thrombocytes* does not show definite and

characteristic changes and the same holds true for the *fragility of red blood cells*.

As to the *mechanism of the CO polycythemia* it appears that it is predominantly due to a stimulation of the hemopoietic system which with continued exposure may result in permanent injury and anemia as illustrated by reports of clinical pictures similar to pernicious anemia. Many investigators assumed that the polycythemia is an attempt of the organism at compensation similar to the increase of red blood cells observed at high altitudes, but as just indicated and as pointed out by Gerbis[1] and Reinhold[1,1] this temporary compensation may result in permanent injury of the blood forming organs. Furthermore Brieger[177,11] found in dog experiments that polycythemia did not prevent the appearance of noxious effects on the circulatory and nervous system. It should be pointed out that in acute CO poisoning other mechanisms possibly may be involved in the hyperglobulemia as discussed by von Oettingen and that it may also be of central origin as demonstrated by Schulhof and Matthes[1] in rabbits and as observed clinically by Dittmar.

It appears therefore that whichever of these mechanisms is involved in the production of polycythemia from CO poisoning this phenomenon is not merely an attempt of the organism at compensation but the outcome of the effect of CO on vital and delicate structures. For this reason polycythemia should be considered as an alarm signal rather than as a physiological and therefore harmless compensation mechanism.

No matter which organs are mostly affected in CO poisoning it appears that injury of the circulatory apparatus is the most outstanding phenomenon.

The behavior of the *blood vessels* varies with different stages of CO poisoning and also with different parts of the body. Many investigators reported vasodilatation especially in the nervous system and it has been assumed that this is due to an atonic condition of the vascular musculature leading to stasis and subsequent tissue damage because of anoxia. As shown by Yant, Chornyak, Schrenck and Patty and others this vasodilatation is not uniform and especially in slow CO poisoning extremely dilated and collapsed blood vessels may be seen in certain sections of the brain. It is obvious that such extensive vasodilatation and vascular injury may lead to hemorrhages in almost any organ as described by various observers (von Oettingen).

The behavior of the heart in CO poisoning has been much discussed. In CO poisoning there is often a tendency to heart failure and as pointed

out by Teleky[185], heart failure occurs more readily in CO poisoning than in any other form of anoxemia. Although in the opinion of many students of the subject, cardiac disturbances are often overlooked because of the predominance of nervous symptoms, they are more frequent after prolonged subacute poisoning than after acute poisoning, but with the latter they may appear after some time has elapsed and may be considerably aggravated by physical exercise. There is no experimental evidence on a direct injurious effect on a perfused heart and for this reason cardiac disturbances must be due to some secondary action. It has been shown experimentally that in CO poisoning the action of the heart is reduced, and that there is a tendency of the heart to pass into ventricular fibrillation. Gay[186] suggested that the heart action may be impaired by dysfunction of the cardiac muscle, by irregularities of the blood supply and by disturbances of the innervation.

There is some experimental evidence that high concentrations of CO may cause cardiac failure by anoxia of the heart muscle leading to cardiac dilatation indicating weakening of the cardiac muscle which presumably is secondary to vasomotor failure. It is not necessarily affiliated with histological changes in the cardiac muscle as shown by the report of Pulvertaft[187], but other observers Weicksel[188] and Monaui[189] noted myocardial damage in cardiac dilatation in delayed CO poisoning. Observations in experimental animals (Campbell[190], Valchera[191]) and clinico-pathological findings reported by Gay[186] show that the increased amount of energy required by the heart in subacute prolonged CO poisoning may result in hypertrophy of the cardiac muscle.

Electrocardiographic studies made in animals exposed to various concentrations of CO as reported by several investigators (Christ[192], Castrovilli[193], Rostelli[194], Drabkin, Lewey, Bellet and Ehrich[195], Ehrich, Bellet and Lewey[196]) show that these will show certain abnormalities indicating some latent damage, and this may be present even in absence of abnormalities in their behavior. In man Kroetz[197] and Steinmann[198] observed irregularities of the electrocardiogram indicating myocardial dysfunction which in the majority of the cases were of temporary nature. Similar disturbances were noted by Colvin[199] and Beck and Suter[200]. Stearns, Drinker and Shaughnessy[201] studied [illegible] cases of CO asphyxia and found that the most common phenomena were abnormalities of the T wave or changes in the level of the S-T segment. There were 4 instances of paroxysmal auricular fibrillation, 1 each of transitory heart block and premature auricular contraction, 2 each of premature ventricular contraction and variations of the P wave and 3 cases

of low voltage of the first lead of the electrocardiogram They assumed that these changes were only of a temporary character and that in several instances they may have been due to other causes and only aggravated by CO anoxemia Loeper Varay Cotter and Leveille[9] analysed the findings in 38 victims of CO poisoning and found changes of the QRS interval and alterations of the T waves in 1 instances diphasic lowering of the P wave in 5 changes of the ST interval and deviation to the left in 2 cases and low voltage and auricular fibrillation in 1 patient each whereas only 3 patients had a normal record In the opinion of Breu[7] it is not so much the concentration of CO in the blood but the duration of the exposure which determines lasting changes of the electrocardiogram

The question as to whether or not CO poisoning may result in injury of the *coronary arteries* has not been definitely answered Kroetz[94] mentioned 6 cases of coronary thrombosis observed 24 to 7 hours after moderate CO poisoning Two similar cases were reported by Nagel[95] Symptoms indicative of coronary injury such as palpitation irregularities of the heart beat and others have been reported by Litzner[96] Beck and Suter[99] Beck Schulze and Suter[97] and others Rastelli[191] assumed that injuries of the coronary arteries as observed in CO poisoning were due to damage of the endothelial lining of the coronary arteries With regard to the behavior of *the pulse rate* this seems to be mostly increased in slow and moderate CO poisoning whereas higher concentrations of CO may cause sudden and distinct slowing of the heart beat associated with low blood pressure

As indicated by many clinical reports and as found by Loeper Vary Cottet and Leveille[20] the *blood pressure* frequently is lowered in CO poisoning Whereas this hypotension usually is of temporary nature occasionally it may be of long duration and then it indicates an unfavorable prognosis as suggested by the reports of Zondek[26] and Steinmann[193] Hypertension on the other hand is less common and its affiliation with CO poisoning was doubted by Koelsch[9] whereas Groetschel[89] and Weil[19] believed that it may result from an irritation of the midbrain by CO

It appears therefore that in CO poisoning the circulatory system may be affected in different ways In most cases of CO poisoning there is more or less marked vasodilatation resulting in a fall of the blood pressure and leading to hemorrhages either by rupture of the vascular walls or by diapedesis The fall of the blood pressure may be aggravated by failure of the heart caused by injury of the cardiac muscle and the

conductive system by anoxemia The injury of the heart muscle may lead to dilatation of the heart With slow and moderate poisoning the heart rate may be accelerated but in severe poisoning it may be slow

Behavior of Nervous System and Sensory Functions in CO Poisoning

One of the first symptoms of CO poisoning is *headache* which sooner or later is associated with fatigue irritability and sleepiness and progressive weakness The headache is first of the frontal type presumably due to vasodilatation in the sinuses but later it extends also to the base of the skull It should be considered as one of the earliest alarm signals should caution against further exposure and should be treated immediately (fresh air) in order to prevent deleterious effects In the first stage the patient may appear to be intoxicated and this may be of medicolegal importance as illustrated by the report of Bell[11]

The behavior of *the spinal pressure* is of considerable importance and should deserve more attention Frequently it is increased in CO poisoning and often associated with a lymphocytosis in the spinal fluid The increase probably is due to the vasodilator action of CO and is not necessarily indicative of cerebral edema

Hyperemia and increased permeability of the cerebral blood vessels may also lead to a condition similar to *hemorrhagic meningitis* It was observed by Beck Schulze and Suter in 8 6 per cent of a group of 150 patients suffering from CO poisoning

One of the most characteristic sequelae of CO poisoning resulting in unconsciousness is complete *amnesia* for the time of the accident which is pointed out by Meyer[212] is often associated with agnostic aphasic and apractic disturbances which are not necessarily due to localized lesions.

Psychoses as sequelae of CO poisoning have been observed repeatedly Usually they develop after apparent recovery from the acute exposure Occasionally this latent period before the onset of psychic disturbances may be absent In a study of 1,000 cases of CO poisoning Shillito Drinker and Shaughnessy[13, 14] noted great variations in the length of this latent period They found that in some persons psychic disturbances may appear within 1 week and in others they may appear after a clear period of from 1 to 3 weeks These psychic changes characterized by confusion and bewilderment combined with loss of memory are mostly of temporary nature Cot and Guilleman[15] stated that the majority of 185 cases of CO poisoning showed no sequela except

temporary headache 8 showed nervous disturbances of which 20 had isolated defects of the memory 1 had mental confusion and 7 developed pareses or paralyses From the report of Shillito Drinker and Shaughnessy [13 214] covering 21 000 cases of CO poisoning it also appears that the prognosis of CO psychoses generally is not alarming since of this entire group only 43 suffered sufficiently severe after effects to necessitate their admittance into an institution and in the opinion of these authors even these stood a good chance for recovery within 2 years Twenty three of these recovered completely 9 suffered permanent nervous and psychic sequelae and 11 died Telely [15] who reported on the fate of about 650 cases of CO poisoning stated that 5 out of 9 more seriously poisoned persons later developed brain symptoms Other students of the subject are however less optimistic With regard to the relation between the severity of the poisoning and prognosis of psychic disturbances Meyer [1] pointed out that the severe initial symptoms are not always indicative of a bad prognosis and that severe injuries are more readily produced by repeated exposure It is difficult to appraise the extent to which the neurological and psychic disturbances depend upon the intensity of the exposure Van Amberg [16] who studied this question in 15 patients suffering from sequelae of CO poisoning believed that patients poisoned with CO are not likely to suffer serious after effects if they recover consciousness within 1 hour after removal from the toxic atmosphere

The question often arises as to whether or not mental disturbances observed subsequent to CO poisoning are the direct result of the poisoning or only the eliciting factor of a latent psychosis In some instances the cause of the psychosis has been not CO but an existing syphilitic infection In others chronic alcoholism arteriosclerosis or hereditary influences may be the fundamental cause Of 528 cases of acute CO poisoning studied by Shillito Drinker and Shaughnessy [2 214] 16, were *hospitalized after emergency treatment* Two thirds of these patients gave evidence of pre existing psychosis acute alcoholism or serious organic diseases and 8.6 per cent had attempted suicide In this study the incidence of mental and nervous after effects of acute CO poisoning was found to be 0 56 per cent It is therefore obvious that in many instances of suicidal CO poisoning there is a psychotic predisposition but in other instances this does not explain the mental and psychic changes observed as sequelae of CO exposure As will be shown in a later section there are certain lesions in the brain which may be considered pathognomonic for CO poisoning and it can be stated definitely

that severe and protracted CO poisoning may result in mental and psychic disturbances

Psychoses following CO poisoning may have a *depressive character* in the beginning and may later change to a *manic type* However this is not a strict rule and cases in which the depressive phase persisted have been reported In the opinion of Giese[17] the Korsakow syndrome is not uncommon as a sequela of CO poisoning A similar statement was made by Seelert[10] who pointed out that this complex is sometimes preceded by a stage of motor unrest and delirium As shown by a report of Mattauschek[19] the Korsakow syndrome may be followed by a manic condition and in spite of the severity of the symptoms complete cure may be the outcome

Of *motor disturbances* convulsions are observed occasionally as sequelae of CO poisoning and these may vary in intensity with the degree of exposure It appears that they are not always due to general asphyxia but are sometimes due to a localized disturbance in the brain Paralyses following CO poisoning are in many instances caused by hemorrhages in the motor centers of the brain and their prognosis depends upon the extensiveness of the extravasations They may result in hemiplegia affecting only one limb or both legs

Muscular spasms and *trismus* have been reported quite often as sequelae of CO poisoning They may be localized in certain muscle groups or there may be general tonic convulsions and even opisthotonus While these phenomena are of a more acute nature in other instances they may be the outcome of more profound cerebral lesions and may assume the picture of katatonic hyperkineses and akinetic stupor and of Parkinsonism Grinker[8] who described such a case of Parkinsonism assumed that the primary cause was vascular paralysis and subsequent asphyxia of certain structures in the midbrain with relatively poor capillary supply The same view was expressed by Meyer[3] who pointed out that the characteristic picture of rigor with akinesis originating in the globus pallidus but without hyperkinesis and vegetative side symptoms may be complicated by symptoms arising from the basal ganglia Stiefler[1] reported a similar case resulting from exposure to war gas and also possibly to CO and he assumed that liver damage followed by degenerative lesions in the brain similar to those observed in Wilson's disease was the primary cause Cases of CO poisoning resembling multiple sclerosis were reported repeatedly

Occasionally CO poisonings have been considered as a cause of *epileptic* or *epileptiform attacks* This question was discussed by

Schiersmann Two cases of *chorea minor* as a sequela of CO poisoning have been reported It appears that the literature on this subject is scanty but Leschke claimed that it is not as rare as is usually assumed *Abnormalities of the speech* and *aphasia* have been observed repeatedly as sequelae of CO poisoning They form part of the picture of Parkinsonism and multiple sclerosis

Apraxia as a sequela of CO poisoning has been reported in connection with other symptoms

More common than speech disturbances are affections of the *eyesight* and *of the oculo motor apparatus* a review of which was published by Wilmer Cases of *amblyopia* as a sequela of CO poisoning are not infrequent Wilmer pointed out that unlike other poisons such as methanol and nicotine CO does not show a great predilection for exerting its toxic effects on the optic nerve fiber as a whole or even on the very sensitive papillo macular bundle He believed that optic nerve lesions may be due to changes in the delicate structures of the nuclei of origin of these nerves Koslowski reported on a patient suffering from visual disturbances characterized by temporary amaurosis and later homonymous hemianopsia followed by recovery after a period of weeks He believed that the site of the injury was the right geniculate body its neighborhood or the internal capsule caused by angiospasm or hemorrhages in these regions

The behavior of the *pupils* in CO poisoning is quite irregular In deep coma they are sometimes contracted sometimes dilated and their reaction to light may vary from case to case and from time to time It appears therefore questionable whether their behavior is of great prognostic value

Nystagmus evidently is not uncommon in CO poisoning and has been reported repeatedly According to Dibelius[6] it may be observed as an early symptom at a later period and it is usually of temporary nature but it is by no means a constant phenomenon in CO poisoning Other disturbances of the ocular motor apparatus such as a *paralysis of the oculo motor muscles diplopia* and *blurred vision* have been reported repeatedly

Affections of the *color vision* are not uncommon in CO poisoning as indicated by the reports of Abelsdorff and Pilman who studied visual disturbances in 70 cases of CO poisoning In Pilman's experience the disturbance began with a contraction of the field for green followed gradually by that for red blue and white and it finally resulted in complete loss of the central color vision

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Occasionally CO poisonings have been considered as a cause of *epileptic* or *epileptiform attacks* This question was discussed by

suggested that the vertigo might be due to hyperexcitability of the labyrinth which is one of the characteristics of subacute CO poisoning

Rutenburg[34] found that 5 out of 15 cases of severe acute CO poisoning developed disturbances of the static and vestibular apparatus during the 24 to 48 hours following the exposure. Five others showed symptoms referable to the cochlea as indicated by moderate temporary reduction of hearing for whispering and a more or less considerable reduction of the bone conduction. He assumed that these phenomena were the beginning of degenerative changes of the neuroepithelium possibly in connection with disturbances of the liquor secretion. In 10 of the 15 patients vestibular disturbances were noted which might have been of central origin. Three similar cases were reported by Rigaud and Escot.

Fisher and Hasse[5] reported that in moderate CO poisoning produced by inhalation of CO in concentrations of 200 to 540 p p m over a period of 40 to 60 minutes the labyrinth in most instances showed an increased excitability as indicated by the more rapid onset and longer duration of nystagmus upon caloric stimuli and by the lowering of the threshold for electric stimuli. Radmark[41] found that of 387 persons suffering from generator gas poisoning 83 suffered from vestibular affections of various intensity. Similarly Lumio[40] found among 1 84 cases of suspected CO poisoning 613 patients who showed oto neurological symptoms 64 9 per cent showing dissociated vestibular reactions 5 per cent central vestibular tonus differences 1 1 per cent a pathological nystagmus response and 0 5 per cent deviation of the eye. Mild symptoms disappeared within 1 to 4 months the moderate symptoms within to 6 months and severe symptoms after 4 to 10 months

Disturbances of other sensory functions *such as taste* and *smell* have been noted occasionally (Roth and Herman[7])

The behavior of the *reflexes* is very variable and evidently independent of the intensity of the exposure but depend upon the character and distribution of different lesions in various parts of the central nervous system

Peripheral neuritis as sequela of CO poisoning is evidently not exceptional and usually develops after an interval of days weeks and even months following the exposure. They are characterized by rheumatic pains sensitivity to pressure on nerves and certain muscle groups sensory disturbances and degenerative reactions. They may lead to atrophic changes and are not necessarily associated with lesions of the central nervous system but may be of peripheral origin. In many in

Optic neuritis as a sequela of CO poisoning alone or as part of the picture of polyneuritis and anomalies of the *retinal eyeground*, edema and inflammatory reactions of the papilla, were observed repeatedly. According to Weissberger hemorrhages in the eyeground are not uncommon in CO poisoning.

In the opinion of Wilmer most of the visual disturbances are the outcome of ocular congestion such as occurs in true anoxemia and as shown by Goldmann and Schubert narrowing of the visual field may result from degrees of anoxemia which cause no other toxic effects. Evans and McFarland[30] showed that with progressive O_2 deprivation there is an increase of the size of the angio scotoma and a progressive loss in the visual field. They believed that the vasodilatation and the increased blood flow through the head as demonstrated by Gibbs, Gibbs and Lennox[31], may result in an increase of the intracranial pressure and in edema.

It appears therefore that some visual disturbance observed in CO poisoning may be explained on the basis of circulatory disturbances and by anoxemia produced by reduction of the amount of oxyhemoglobin. The more lasting and especially the permanent injuries are presumably caused by lesions in the nuclei of the optic nerve and possibly by cortical injuries.

In aviation medicine the effect of low concentrations on the visual functions is of great interest. McFarland, Roughton, Halperin and Niven found that the effect of CO on the visual threshold at higher altitude is somewhat greater than would be expected from the same degree of CO hemoglobinemia. According to Lilienthal and Fugitt[33] increment in CO hemoglobin of the order of 5 to 10 per cent result in an appreciable deterioration of the flicker fusion frequency at altitudes which alone did not affect the flicker fusion frequency (5,000 and 6,000 feet).

Symptoms referring to the *ear* and *the vestibular apparatus*, such as tinnitus and vertigo are among the characteristic early phenomena of CO poisoning. Partial or complete deafness subsequent to CO poisoning has been reported occasionally. Alt[34] assumed that inflammatory degenerative changes of the acoustic nerve were responsible for auditory disturbances characterized by reduction of bone conduction and some impairment of hearing. He also considered the possibility of multiple ecchymosis in the nerve end apparatus of the cochlea and vestibulum. In one of his cases these disturbances were of a temporary nature but in the other they persisted over a considerable period of time. Lowy

Voss[44] increases the function of the thyroid causing the clinical picture of cerebral thyreotoxicosis

Regarding the effect of CO on the *pituitary gland* Nicoletti[4] found that it may cause a mild state of hyperfunction Kampelmann and Schulze[16] observed a decrease in the amount of thyreotropic hormone in the anterior lobe as determined by bioassay and Patterson Smith and Pickett[4] found that after repeated moderately acute CO poisoning of rats the hypophysis contained vacuolated and enlarged basophilic cells An involvement of the pituitary gland in CO poisoning is indicated also by the report of Girault and Richard[10] and others who reported on a marked increase of urinary excretion simulating diabetes insipidus as a sequela of acute CO poisoning

Many clinical observations indicate that the *adrenals* are affected in CO poisoning Starkenstein[18] noted histological changes indicative of hyperfunction in animals poisoned with CO Nicoletti[4] observed a hypofunctional state of the adrenal cortex paralleled by a hyperactivity of the medulla in acute CO poisoning Hypertrophy of the adrenal marrow also was reported by Stemmler and Parade[13] in a miner who died from hypertension and hyperthyroidism after repeated subacute CO poisonings That the condition may vary with the type of exposure is suggested by the report of Peisachowitsch[0] who saw an exhaustion of the chromaffine substance with short and acute exposure to CO and hyperfunction of the adrenal marrow with subacute exposure He assumed that the exhaustion is due to an increased output of epinephrine With repeated poisoning there also were retrogressive changes of the cortex not seen with single short exposures and in addition disappearance of the chromaffine material and distinct signs of atrophy of the organ Similar variations of the histological picture were reported by Lissachowitsch[1] and Schmelzer[2] who found that in subacute CO poisoning hypo and hyper functional changes may run parallel whereas with continued exposure to very low concentrations signs of hyper function are prevalent

Many investigators have noted that in CO poisoning the *salivary* excretion is markedly increased and Starkenstein[249] affiliated this with a sympathetic stimulation which is perhaps secondary to the increased output of epinephrine

Animal experiments indicate that exposure to CO may impair the *sexual functions*, and Riedel[3] reported 3 cases of subacute poisoning who aside from other symptoms from the nervous system suffered from such disturbances and various abnormalities of the spermatozoa

stances mechanical trauma and pressure on the nerves may be contributing factors and hemorrhages may play an important role in their genesis. These may act by pressure on the nervous tissue or cause bloody imbibition of the peri- and epi-neurium leading to scar formation and ischemia of the nerve fiber. In other instances peripheral neuritis may be associated with disturbances of the conduction in the pyramidal tract and of the bulbar nuclei caused by hemorrhages or primary degenerative changes in the ganglionic cells.

The behavior of the *body temperature* may vary considerably with different patients. In acute poisoning it may be lowered because of lowering of the metabolism or because of circulatory failure. More frequently it is, however, increased and this may be indicative of injury in the midbrain. It may last only a few days and be associated with metabolic disturbances such as glucosuria.

Effect of CO Poisoning on Gastrointestinal Tract and Uropoietic System

Symptoms from the *gastrointestinal tract* are mainly characterized by diarrhea and bloody stools which may be due to hemorrhages into the intestine and there may be moreover nausea, vomiting and abdominal pain and symptoms simulating gastric ulcers. Nausea and vomiting may be of central origin resulting from a stimulation of the medullary centers.

Functional disturbances of the *kidney* are not uncommon in CO poisoning as indicated by the presence of albumin and sugar in the urine. Occasionally there may be marked polyuria which may be of central origin because of an affection of the pituitary gland is reported by Girault and Richard[10] and Sanger and Gilliland[11]. Dysfunction of the *urinary bladder* characterized by retention of urine appears not to be exceptional in CO poisoning and it may be caused by some disturbance in the spinal cord is suggested by Beck, Schulze and Suter[0].

Changes of the Glandular Functions in CO Poisoning

With regard to the effect of CO on glandular functions *hyperactivity of the thyroid* has been observed repeatedly in CO poisoning. Regarding the mechanism of this disturbance Bader[4, 43] assumed that this was due to a toxic effect on certain colloid containing glandular cells in the mesencephalon, the stimulation of which, as shown by

reaction The *more shallow respiration during the period of uncon* sciousness chilling during the exposure and changes of the permeability of the capillaries may be contributing factors Drinker and Cannon[illegible] found that among a number of unconscious victims of CO poisoning 37 per cent had abnormal amounts of moisture in the respiratory tract and 9.4 per cent developed pneumonia In those cases where pneu monia is observed at a later period especially in those instances where *the patients* are *unconscious* and *suffer from symptoms* similar to Park insonism and multiple sclerosis or where the poisoning is complicated by vomiting foreign material may enter the respiratory tract and lead *to pneumonia*

Pulmonary edema and hemorrhages in the lungs and in the pleura occasionally combined with bloody serous exudate in the pleural cavi ties may be explained also on the basis of circulatory disturbances

Effect of CO on Metabolism

The effect of CO on the circulation respiration nervous system and glandular functions is partly reflected in its effect on the metabolism

Much attention has been paid to the effect of CO poisoning on the *carbohydrate metabolism* Glucosuria as a sequela of CO poisoning has been observed by many clinicians and experimenters Leschke[33] saw it in 8 per cent of his cases of CO poisoning and Zangger (quoted from Leschke[illegible]) believed it to be present in 20 to 30 per cent of patients suffering from CO poisoning In a series of 34 cases Moeschlin[illegible] noted in 57 per cent a noticeable increase of the blood sugar which persisted 24 to 48 *hours in the majority* of the cases 78 *hours in* instances and 8 days in 1 patient Although the incidence of glucemia was more fre quent in severe than in light cases of CO poisoning a definite relation ship between the blood sugar level and the severity of the exposure could not be established

The mechanism of this glucemic action has been investigated re peatedly and several factors appear to be involved in this phenomenon *and it seems not unlikely that it may be produced in several ways*

The presence of fever and diuresis in CO poisoning which has been affiliated with stimulation of certain centers in the midbrain also sug gests glucemia and glucosuria of *central origin* but since it is not inhib ited by the administration of chloral hydrate as is the case in glucemia following puncture of a certain section of the midbrain it appears that

Effect of CO on Respiration and the Lungs

The effect of CO on the *respiration* varies considerably with the intensity of the exposure Haldane[1] noted in self experiments that hyperventilation of the lungs begin at a concentration of about 35 per cent CO hemoglobin On the other hand Sayers Yant Levy and Fulton[3] and Hayhurst[3] stated that the clinical picture of CO poisoning is not associated with irregularities of the respiration Asmussen and Chiodi[4] pointed out that there is a marked difference between the effect on the respiration of anoxemia due to reduction of O in the inhaled air and a similar degree of anoxemia due to CO When 20 to 30 per cent of the hemoglobin is saturated with CO subjects show the same behavior with regard to ventilation of the lungs as normal persons whereas persons suffering from a similar degree of anoxia from lack of O in the inhaled air show a greater degree of ventilation They believed that not the reduction of the O content of the blood but the reduction of the O tension in the blood (which is not affected by CO) is the cause of the hyperventilation by an action of the reduced p O on the carotid body Similarly Chiodi Dill Consolazio and Horvath noted no hyperventilation either in human subjects or in unanesthetized dogs even though in some instances the concentration of CO hemoglobin in the blood reached 52 per cent and presented evidence that in CO poisoning the respiratory center is depressed It appears therefore that in cases of CO poisoning in which the respiration is increased this increase is due to interference with the oxygenation of the blood resulting in a decrease of the O tension of the blood In the absence of circulatory disturbances and with unhampered O exchange in the lungs the respiration may be depressed in CO poisoning

As pointed out by Thompson[58] affections of the respiratory tract especially of the *lungs*, are not infrequent in CO poisoning In those instances where the poisoning results from the inhalation of fumes from fires they may be due to irritant gases such as nitrogen oxides In other instances early injury of the lungs may be due at least in part to the inhalation of fumes of metal oxides Oliver[7] observed a high incidence of early pneumonia especially of the lobar type, in miners suffering from CO poisoning without such complications as resulted from the Courriere disaster Similar cases were reported by Hatton in the Hulton Colliery explosion were observed during World War I and were reported by others In such instances it appears that circulatory failure is mainly responsible for the stasis and subsequent inflammatory

even in the presence of a high percentage of CO hemoglobin and in prolonged subacute poisoning the skin may be pale and of leaden appearance

Erythema of the skin is not uncommon in CO poisoning and occasionally a *papular dermatitis* has been observed *Localized edema* of the skin has been observed repeatedly and this may be associated with and result from neuritis or with circulatory disturbances such as stasis and hemorrhages and petechiae Not infrequently *blisters of the skin* are seen in CO poisoning which probably are the result of nervous injuries The vitality of the skin may be seriously affected in CO poisoning as indicated by the great tendency toward the development of *decubitus* which by some clinicians has been considered as pathognomonic of CO poisoning and which may easily lead to septicemia It may be due to nervous and vascular injury and it may result in gangrene of smaller or larger sections of the body

In acute and severe CO poisoning the *musculature* may offer the picture of myositis which may pass into fatty degeneration and which probably is the outcome of circulatory disturbances vascular injury and anoxia of the muscle tissue

Question of Chronic CO Poisoning

There is at present considerable controversy as to whether or not there is a chronic CO poisoning largely depending upon the interpretation of the word chronic As pointed out by Ellinger [6] chronic *poisoning usually means the repeated or continued administration of* small quantities of a poison resulting finally in toxic symptoms In this the single dose must be so small that it does not cause detectable effects In addition the damage produced by single or repeated doses may be additive and result finally in the toxicological picture of a poisoning In the case of CO we have no evidence that CO as such or in combination with other compounds remains in the tissue for any considerable period of time and so far there is no evidence that concentrations of CO which cause no acute subjective or objective symptoms will affect any structures of the organism in such a way as may lead to functional or permanent injury Many students of the subject assume the possibility of chronic CO poisoning but in some of these cases acute symptoms were observed and in others possibly were overlooked on account of the vagueness and inconspicuousness of their character It appears

a peripheral mechanism must be at least partly involved in the production of this phenomenon

It has been shown that the CO glucosuria can be prevented by ligation of the coeliac and mesenteric arteries, by starvation and the administration of insulin so that it appears that CO glucemia and CO glucosuria are bound to the presence of adequate glycogen depots in the liver and according to Straub[71] it is also bound to the presence of available proteins It appears further that it is bound to the responsiveness of the central nervous system the responsiveness of the sympathetic nerves and that the adrenals are involved in this reaction, the stimulation of which may be of central origin In addition the hyperfunction of the thyroid in CO poisoning may affect the carbohydrate metabolism (von Oettingen[4])

In many instances of acute severe CO poisoning the increase of the blood sugar level outlasts other phenomena and this evidently is not directly related to the concentration of CO hemoglobin in the blood or to a temporary anoxemia in such cases the glucemia may be due to a decreased permeability of the kidney In other instances the hyperglucemia appears to be of short duration

With regard to the effect of CO on the *nitrogen metabolism* it has been found that in acute CO poisoning the urinary excretion of nitrogenous compounds may be markedly increased and that this may last for a considerable period of time the same holds true for the uric acid level in the blood whereas the creatinin level is only slightly affected if at all

There is little information on the effect of CO on the *oxygen metabolism*, but numerous experimental studies with animals indicate that this may vary considerably with the intensity and duration of the exposure and it appears that in acute CO poisoning there is a reduction of the alkali reserve that is a reduction of the CO binding power of the blood It does not appear to be established whether this is due to an actual decrease of the blood alkali or to a reduction of the available reducible hemoglobin which as shown before plays an important role in the liberation of CO

Behavior of Skin and Musculature in CO Poisoning

Usually it is stated that in CO poisoning the *color of the skin* is pink with a cherry red hue but this is not an absolute rule It may be absent

even in the presence of a high percentage of CO hemoglobin and in *prolonged subacute poisoning* the skin may be pale and of leaden appearance

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that there is probably no chronic poisoning in the sense of toxic effects from continued exposure to acutely non toxic concentrations of CO whereas chronic effects from toxic exposures have been observed frequently Such diagnosis should however, be based on an existing exposure to CO and if possible on the presence of CO hemoglobin in the blood

Such subacute CO poisonings are apparently not uncommon and it may be that in many less characteristic cases CO is not recognized as the causative factor Moderate subjective symptoms such as headache tinnitus hammering in the temples oppression in the chest and slight vertigo are liable to disappear promptly upon discontinuation of the exposure while with more prolonged exposure it may take more time and occasionally therapeutic measures to overcome these toxic effects Headache vertigo fatigue sleepiness during the day sleeplessness during the night nervousness irritability inability to concentrate lack of memory and mental instability are the most common nervous symptoms Sensory disturbances of various types appear to be less common and motor disturbances are comparatively rare Tremors of varying intensity atrophy of certain muscles and muscle groups and visual disturbances have been observed occasionally Symptoms from the gastrointestinal tract such as lack of appetite nausea vomiting and diarrhea are more common and they may lead to emaciation and may be associated with intestinal hemorrhages and ulcers There may be slight injury of the kidney as indicated by albuminuria The skin frequently shows pallor, which may be due to vasoconstriction and not caused by anemia although the latter has been observed occasionally Changes of the circulation such as irregularities of the pulse rate blood pressure changes palpitation and precordial distress have been reported repeatedly

Regarding the incidence of the various signs and symptoms affiliated with so called chronic CO poisoning Beck[63] believed that headache is the most outstanding symptom since it was present in 58 out of 97 of his cases In 46 instances this was associated with vertigo and in 30 with weakness and ataxia of the legs Fifty-two out of 97 complained of weakness many of these were confirmed neurotics and some definitely psychotics Nervous manifestations such as a feeling of depression restlessness anxiety fears introspection emotional upheavals drowsiness and insomnia were quite frequent Thirty-six out of 97 suffered from paresthesias of the extremities occasionally tinnitus and disturbances of the sense of smell Neuromuscular manifestations such as cardiospasms were observed in 6 instances pylorospasms in 1 enterospasms in 3, anal

spasms in 3 urethral spasms in muscular spasms of the legs in 14 and fibrillary twitchings in 6 As abnormalities of the gastrointestinal tract achlorhydria was observed in 5 subacidity in 19 and hyperacidity in 7 cases of a group of 59 patients studied in this respect and 16 patients suffered from nausea and vomiting anorexia being quite frequent Regarding cardiorespiratory manifestations dyspnea and palpitation were the most common symptoms Fourteen patients complained of cardiac distress of varying degree and suffered from typical angina pectoris and symptoms of heart block Generally there was a tendency toward slowing of the pulse rate and lowering of the blood pressure In 30 patients the basal metabolism was found to be significantly low Forty four out of 97 showed an increase in the number of red blood cells to above 5 000 000 In one instance these reached 7 800 000 and the hemoglobin varied from 100 to 110 per cent while the white blood cell count showed no noteworthy abnormalities With regard to manifestations of the urinary system vesical irritability with tendency to nocturia dysuria and pollakiuria was quite common and 13 patients suffered from glucosuria and 12 from albuminuria Menstrual disturbances of various kinds and in males diminution of the libido and impotence were observed occasionally In a later publication Beck [4] stated that of 784 gas heaters or stoves in 1 5 homes 1 per cent were discharging CO into the room In 10 per cent of the cases this amounted to 300 parts per million of CO or more in 5 per cent to 750 parts per million or more and in 3 per cent to 1 500 parts per million or more It appears therefore quite possible that persons suffering from chronic CO poisoning may have had a considerable exposure

Pathological Changes in CO Poisoning

The variations in the clinical picture of CO poisoning are reflected in the multiplicity of the pathological changes found in various organs

The pathological changes of the *circulatory system* are mainly characterized by injury of the blood vessels and the heart It has been pointed out before that in CO poisoning the *blood vessels* undergo functional changes and these may result in degenerative changes which are characterized by parenchymatous changes in media and intima They may consist in thickening of the arterial walls swelling loosening and degenerative changes of the vascular membrane and complete destruction of their nervous elements The final outcome may be calcification

The changes of the *capillaries* are much less conspicuous It is obvious that such changes of the blood vessels may lead to the formation of thrombi and emboli the presence of which has been reported repeatedly and to *hemorrhages*, which may be found in various organs With regard to pathological changes in the *heart* it appears that hemorrhages in the cardiac muscle are not very common Necroses may be found in such sections which develop the greatest amount of energy during the cardiac contraction and therefore are most liable to suffer from anoxia Acute degenerative changes of the cardiac muscle have been reported repeatedly

With regard to pathological changes of the *nervous system* these may be found in the brain and in the peripheral nerves The morbid changes in the brain consist most frequently in hyperemia, which may result in bloody exudates between the meninges, hemorrhages and cerebral edema The *cerebral cortex* may show diffuse proliferation of the glia of the marrow fibers and degenerative changes in the third and fourth layer of Brodmann In accordance with such symptoms of CO poisoning as tinnitus, stiffness of the neck and muscular rigidity *bilateral softening of the lenticular nucleus* is quite frequent and these changes are said to differ from those observed in progressive lenticular degeneration in that with the latter the changes are mainly located in the putamen while in CO poisoning the pallidum is affected most Similarly degenerative changes in the *globus pallidus* are quite common whereas those in the *thalamic region* appear to be less frequent and those in the *nucleus candatus* and *nucleus dentatus* are rather rare Degenerative changes in the *corpus striatum* appear to be more frequent With regard to degenerative changes in the *basal ganglia* those of the vagus are said to be more frequently affected than those of the facialis and of the optic nerve In addition to these changes the deeper sections of the white matter may show diffuse reactions as reported by numerous investigators

In contrast to the cerebral findings degenerative changes in the *spinal cord* are less common

With regard to pathological changes in the *peripheral nerves* these have been observed in cases of peripheral neuritis as sequelae of acute CO poisoning These may have been the outcome of a direct toxic effect on the nerve or the secondary result of vascular damage

With regard to pathological changes in *liver* and *kidney* these have received much less attention Degenerative changes in the liver seem to be quite rare whereas turbid swelling hyperemia inflammation and necrotic changes in the kidney are somewhat more common

Mechanism of CO Poisoning

Most investigators assume that the toxic effects of CO are due solely to its great affinity to hemoglobin and that it acts exclusively by interfering with and finally inhibiting completely the oxygen supply There are however indications that in addition to its anoxemic action CO has a direct toxic effect on the central nervous system and there are a number of reactions which may indicate a specific primary or secondary effect of CO on certain heme containing or similar constituents of various parts of the organism as pointed out by von Oettingen[4]

Variations in Susceptibility to CO

It has been claimed repeatedly that women tolerate CO better than men and that children are more susceptible to CO than adults The later is however not substantiated by the toxicological literature because there are several instances of CO poisoning of whole families in which only the small infants survived and experimental findings in animals as reported by Smith McMillan and Mack[6] and Cameron[66, 67] do not support this claim It is therefore questionable whether or not such differences exist because so many different factors may enter into the picture It has been pointed out that the affinity of the hemoglobin to CO varies not only in different species but also in members of the same species and even in the same individual at different times In addition it is obvious that the metabolic rate at the time of the poisoning and the amount of physical exercise prior to during and after the exposure may play an important role Physiological differences in the vascularization the constitution of the blood vessels and the condition of the heart may also be contributing factors It also appears possible that the formation and accumulation of certain iron containing pigments especially in the central nervous system may play some role in the final outcome of such poisoning Finally it should be remembered that it is very difficult if not impossible to state with any degree of certainty whether two individuals found in an atmosphere containing CO actually had the same exposure because of the possible existence of air currents which might lead to the accumulation of CO in certain sections of the room

Question of Habituation to CO

Continued exposure to low concentrations of CO may cause subjective symptoms to become less noticeable as indicated by the reports of Haldane and Lorrain Smith[97] and others As pointed out by Buresch[4] this does not necessarily imply that the specific toxicity of the gas is reduced so that there may be danger that the decrease of the subjective sensitivity to CO may allow somatic symptoms to progress unnoticed That such possibility should be considered seriously, appears to be indicated by an observation of Campbell[6] who noted that after continued exposure to low concentrations mice showed an increase of red blood cells and hemoglobin but nevertheless developed a hypertrophy of the heart and became sterile Similarly Gorbatow and Noro[9] found that rats, exposed repeatedly to low concentrations of CO, developed a tolerance towards the depressant effect of CO on the central nervous system but that their general condition became steadily worse during such exposure It appears therefore, very questionable at best that there is a true habituation to CO

Synergistic Factors in CO Poisoning

The susceptibility to CO poisoning is increased by physical exercise because of the increase in oxygen demand during muscular activity and the potential failure of the heart when this has to function under greater stress under anoxic conditions The same holds true for other conditions which lead to an increased consumption of oxygen such as hyperthyroidism and the increase in oxygen metabolism as produced by dinitrophenol

The susceptibility is also increased when the environmental temperature and humidity is increased as was demonstrated by Sayers Meriwether and Yant[103] and others In the presence of methemoglobin the toxicity of CO is increased because methemoglobin and CO hemoglobin are both unable to convey oxygen to the tissue and the presence of both decreases the dissociation of oxyhemoglobin which effects are additive It is therefore apparent that in the presence of methemoglobin forming compounds such as aliphatic nitric and nitrous acid esters aromatic amines and nitrocompounds the susceptibility to CO may be markedly increased

Many students of the subject agree that artificial illuminating gas is

more toxic than would be anticipated from its percental concentration of CO This may be explained by the presence of various contaminants and of hydrocarbons which in sufficient concentrations will have a depressant effect on the central nervous system

It has been shown that other chemicals which interfere with the absorption distribution and utilization of oxygen increase the susceptibility to CO This has been demonstrated for nitrogen oxide and similar irritant gases the inhalation of which leads to pulmonary edema thus interfering with the absorption of oxygen and with elimination of CO through the lungs and for hydrogen sulfide and hydrocyanic acid which depress the respiratory center and interfere with the utilization of oxygen by the tissue

Pulmonary affections such as anthracosis tuberculosis and silicosis which decrease the pulmonary efficacy may have a similar effect which also holds true for abnormalities of the blood such as chlorosis and anemia

Since as just pointed out one of the fundamental effects of CO is its action on the peripheral blood vessels any condition affecting these structures such as alcoholism arteriosclerosis syphilis and cardiac disorders will increase the susceptibility to CO

Prophylaxis of CO Poisoning

It is obvious that the best preventive of CO poisoning would be the prevention of any pollution of the air with CO which can be accomplished to a very considerable degree by proper engineering methods and adequate ventilation The maximum allowable concentration of CO in air is accepted (American Standards Association [1]) as 100 parts per million of air or as 0 01 per cent by volume (0 11 mgm /l at 25 C and 760 mm Hg) for exposures not exceeding a total of 8 hours per day and as 400 parts per million or 0 04 per cent by volume (0 46 mgm /l at 25 C and 760 mm Hg) for exposures not exceeding one hour daily It should be emphasized that with concentrations greater than 100 parts per million increased physical activity increased humidity *increased CO concentration in the atmospheric air or decreased con*centration of O_2 increase the toxicity of CO so that toxic effects may result more readily from exposure to such concentrations But the recent work of Ehrich Bellet and Lewey [156] on the effect of continued exposure of dogs to concentrations of 0 01 per cent CO in air may

suggest that this limit should be lowered For the prevention of CO poisoning it appears absolutely necessary that the public, especially persons subjected to occupational exposure to CO be instructed regarding the toxicity and potential dangers of CO because a survey of the literature indicates that sources of CO poisoning are frequently not recognized and appreciated properly

Special attention should be paid to safety regulations In entering small enclosures such as fire boxes dust bins etc it should be kept in mind that CO may accumulate in the upper sections Whenever a person must enter an enclosure in which the presence of CO is suspected he should wear a safety line and an open air respirator and during his stay there he should be watched by a crew of men familiar with the dangers signs and symptoms of CO poisoning

With regard to the use of canister gas masks for the prevention of CO poisoning it should be pointed out that they all have a comparatively short life that their effectiveness is bound to the presence of adequate amounts of oxygen in the air, and that they often protect only against certain concentrations of CO For this reason it appears desirable as already indicated to use open air masks for routine work and to resort to canister masks only in case of emergency

In view of the toxic effects of CO on the circulatory and nervous systems a proper selection of personnel is also of paramount importance Persons suffering from diseases of the vascular system such as arteriosclerosis organic heart diseases, and especially persons with cardiac insufficiency anemic conditions nervous disorders and syphilis should be excluded from operations in which the danger of exposure to CO is known to exist The same holds true for persons suffering from affections of the lungs such as emphysema anthracosis silicosis and tuberculosis and individuals with an increased O demand, such as pregnant women and persons suffering from hyperthyroidism

Serious sequelae of CO poisoning may be prevented by adequate medical control of the personnel, if any worker who feels the slightest indication of exposure to CO is instructed to have a blood test made for the presence of CO hemoglobin so that the prodromal stage of CO poisoning may be detected and treated properly

The strict enforcement of these regulations not only reduces the incidence of serious injuries from CO poisoning but also aids in the detection of other disabling conditions which otherwise might be credited to the effect of CO

Treatment of CO Poisoning

In the treatment of CO poisoning it is most essential that the victims be removed from the atmosphere contaminated with CO and that no effort be spared to speed up the excretion of CO from the organism because the duration of the anoxemia appears to be the most important factor in the prognosis of CO poisoning In order to accelerate the dissociation of CO hemoglobin and the elimination of CO oxygen should be administered intermittently for 15 20 minutes as soon as possible

Henderson and Haggard[1,2] claimed that during the development of CO asphyxia there is excessive breathing which markedly reduces the body reserve of CO_2 They assumed that on account of this removal of CO_2 which normally acts as a stimulus for the respiratory center the respiration is slow for several hours and the excretion of CO is correspondingly reduced *For this reason they believed that the administration of CO_2 together with O_2 is of paramount importance for the prompt elimination of CO* Drinker[3] concluded from experience with 100 cases of acute CO poisoning that this combination is exceedingly valuable and that in mild cases it relieves or prevents the occurrence of headache and nausea that serious cases still breathing spontaneously revive rapidly and completely and that it may be combined with the prone pressure method of artificial respiration as advocated by Henderson and Haggard[4]

Opinions regarding the therapeutic value of the combined administration of CO_2 with O_2 are not uniform however Sayers and Yant[5] found the administration of O_2 with 8 to 10 per cent CO_2 slightly more effective than that of O_2 but their experience in man and in animals indicates that the O_2 CO_2 mixture gives no better results than pure O_2 alone when judged by the time necessary for recovery after a given exposure to CO and a given saturation of the blood and the condition of the animals or victims after treatment was about the same in both cases (Sayers[273]) Similarly Nicloux Nerson Stahl and Weill[6] found that the effect of CO_2 was not as marked as was assumed by Henderson and Haggard Walton Eldridge Allen and Witherspoon[7] also believed that the combination of oxygen with carbon dioxide offers no very material advantages and the same opinion was expressed by Teleky[185] and according to Speert[5] the addition of 5 to 8 per cent of carbon dioxide to oxygen for the treatment of CO poisoning is no longer recommended by the U S Army

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The strict enforcement of these regulations not only reduces the incidence of serious injuries from CO poisoning but also aids in the detection of other disabling conditions which otherwise might be credited to the effect of CO

In order to secure better ventilation of the lungs a number of mechanical devices for artificial respiration have been developed. Drinker and Cannon[210] made a comparative study of different methods of resuscitation and found no evidence that either the lungmotor or the pulmotor are superior to the manual prone pressure method of artificial respiration and they pointed out that hospital records indicate that any apparatus that drives the air by positive pressure into the lungs may constitute a severe danger to the patient. Drinker, Drinker, Shaw and Redfield[11] found in cats that infected or other materials may be carried into the lungs by positive pressure ventilation. In addition they pointed out that with forced respiration if the mask is not fitted tightly the leak will be closed during the negative pressure period and thus more air will be removed from the lungs than will be blown into them and in this way the efficiency of the pulmonary ventilation may be gradually decreased and the size of the chest will be gradually reduced. It appears however that the well known apparatus for artificial respiration can be used safely if used with adequate caution and surveillance.

Based on the beneficial results made with intravenous injections of procaine hydrochloride in cases of local anoxemia and the success reported by Justin Besançon and Laroche[87] in the treatment of CO poisoning, Olsen, Marinacci, Ray and Amyes[4] and Amyes, Ray and Brockman[5] tried this medication in 23 patients with severe CO poisoning and unfavorable prognosis. Seventeen of these made a good recovery whereas only 6 did not improve or died. It should be pointed out that the latter group had received the injections a long time after the exposure to CO and that early treatment secures better results. In order to avoid allergic reactions the patient should be tested by skin test for sensitivity to procaine and it has been suggested that if the patient is conscious and his respiration is not depressed to premedicate him with some barbiturate such as pentobarbital 0.13 gm intramuscularly especially before the first injection if his tolerance to procaine is uncertain. The injections should be given preferably in doses of 500 mgm (500 cc of a 0.1 per cent solution) of procaine hydrochloride dissolved in 5 per cent dextrose either in water or isotonic saline and injected slowly over a period of 2 hours. In some cases a dose of 100 mgm (as 1.0 per cent solution) was given in about 5 minutes but it appears that the latter procedure is less beneficial. In case of toxic reactions (collapse) it is recommended to give 50 mgm of ephedrine sulfate intravenously and in case of convulsions 0.5 gm sodium

Recently Pace Strajman and Walker [7] showed that in patients with 20 to 30 per cent CO hemoglobin in their blood the half time of the elimination of CO was considerably faster when they were allowed to inhale O under pressure of 2.5 atmospheres for one hour than when inhaling it under atmospheric pressure for the same period of time. They also showed that under these conditions larger amounts of O are dissolved in the blood which may be an important factor in antagonizing the anoxia.

It has been pointed out repeatedly that as soon as the respiration is impaired the administration of O or of O CO mixtures should be combined with *artificial respiration*. According to Murphy and Drinker [4] this should be administered also to patients who are breathing but who are suffering from severe asphyxia. It is possible that undesirable side reactions may result from the indiscriminate and too vigorous use of this procedure especially since the compression of the possibly hyperemic lungs may lead to hemorrhages. Such possibilities indicate that artificial respiration as helpful and even life saving as it may be should be performed with due precaution.

The most commonly used procedure for artificial respiration is the Schafer prone pressure method which is carried out as follows as described by Sayers[2]:

1. Lay patient on his belly one arm extended directly overhead the other arm bent at the elbow and with the face turned outward and resting on the hand or forearm so that the nose and mouth are free for breathing.
2. Kneel straddling the patient tightly with your knees placed at such a distance from the hip bones as will allow you to place the palms of your hands on the small of the back with fingers resting on the ribs the little finger just touching the lower rib with thumb and fingers in natural position and the tips of the fingers just out of sight.
3. With arms held straight swing forward slowly so that the weight of your body is gradually brought to bear upon the patient. The shoulder should be directly over the heel of the hand at the end of the forward swing. Do not bend elbow. This operation should take about two seconds.
4. Now immediately swing backward so as to completely remove the pressure thus returning to position described in paragraph (2) above.
5. After two seconds swing forward again. Repeat deliberately twelve to fifteen times a minute the double movement of compression and release a complete respiration in four to five seconds.

if the condition of the patient fails to improve upon the inhalation of oxygen or carbogen Several of the more common analeptics have been used by different clinicians and there is no evidence that one of them has a definite advantage over the others Cardiac stimulants and vaso constrictor agents which sometimes are used to improve the circula tion should be used only with great precaution because of the possible increase of the spinal and intracranial pressure which may result from their administration

It should be pointed out that atropine and morphine are contra indicated in CO poisoning The former causes some stimulation of the respiratory center by increasing the dead space in the lungs by broncho dilation and by the very same mechanism would tend to interfere with the elimination of CO through the lungs The latter is a depressant of the respiratory center and for this reason would have the same effect

With regard to the use of *methylene blue* in the treatment of CO poisoning it should be pointed out that this is contraindicated and that it may cause severe complications Since methylene blue is a methemo globin former and because the latter is additive in its effect with CO hemoglobin any existing anoxemia may be considerably increased by this medication In addition methylene blue may cause irritation of the gastrointestinal tract restlessness paresthesias pain in the chest and stranguria and its leakage from the vein may cause painful infiltrations

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amytal in 2 to 5 c c of water by the same route In these cases the treatment always was given several hours after the removal of the patient from the exposure and when it was evident that rapid recovery was not taking place or when the patients were suffering from nervous manifestations

In transferring victims of CO poisoning to fresh air care should be taken to avoid chilling because in comatose persons this may result in lowering of the body temperature a marked fall of the O tension in the arterial blood and it may also predispose to pneumonia For these reasons the patient should be wrapped in blankets and if necessary should be kept warm with hot water bottles properly wrapped in covers in order to avoid direct contact with the skin to prevent burns

Since the main characteristic of CO poisoning is an interference with the O supply any physical exercise should be avoided Even after apparent recovery from the acute symptoms any physical strain should be forbidden

It has been pointed out before that one of the primary effects of CO poisoning is a hyperemia of the cerebral blood vessels resulting in an increase of the spinal pressure and edema of the brain The following therapeutic measures aimed at decreasing the cerebral hyperemia and reducing the danger of cerebral edema have been suggested

In order to relieve the circulation in CO poisoning *venesection* has been advocated Occasionally this has been combined with infusion of saline or with blood transfusion but it appears questionable whether this is of real benefit From experience with other forms of gas poisoning leading to pulmonary edema it appears much more reasonable to follow the bleeding with intravenous injections of hypertonic salt or dextrose solutions This will have a favorable effect by itself even without preceding venesection as was demonstrated by Forbes Cobb and Fremont-Smith [8] who noted reduction of the bulk of the brain and relief of compression symptoms in animals and prompt disappearance of headache and of stuporous conditions in man

In severe cases spinal puncture performed repeatedly if necessary may also give relief

The hyperemia of the central nervous system may be relieved also by the administration of cathartics which cause a marked vasodilatation in the splanchnic area and loss of fluid both of which tend to relieve the spinal and intracranial pressure

Regarding the use of analeptic agents their use seems only indicated

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CARBON DISULFIDE

By Alice Hamilton and Rutherford T. Johnstone

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Historical

Carbon disulfide for many years has played an important part in the rubber industry in Europe and a less important part in American rubber manufacture. It is necessary to incorporate sulphur in crude rubber, the process being known as vulcanizing, and this may be done either by adding flowers of sulphur and then heating the mass or by exposing rubber to the action of sulphur monochloride either in vapor form or by dipping it in the liquid or by painting. The carrier for sulphur monochloride usually was carbon disulfide. American manufacturers always have preferred the heat cure for rubber, while the Europeans preferred the so-called cold cure with carbon disulfide. It is this last compound that has given to European rubber manufacture a very bad reputation, and the literature is full of reports of carbon disulfide poisoning in rubber workers. Recently these cases have diminished in number as hygienic conditions have improved, but their place has been taken by a new class of workmen, the makers of artificial silk by the viscose process. This is the process used in Europe and the Orient and also in this country in the production of viscose rayon.

Carbon disulfide was recognized as an industrial poison by the French almost one hundred years before psychiatrists in the United States were willing to do so. Payen[1] who first described its action in 1851 was followed by Delpech[1] in 1856, the latter describing 4 cases in rubber workers and also experimental poisoning in dogs. Germany

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followed with a number of very thorough studies of this poison, whose manifestations were said to be as varied as those of lead (Koester)[1] Then many reports began to come from Italy, some from England, France, Holland, Japan but up to the early years of this century only one article had been published in the United States that of Peterson[13] in 1892 describing carbon disulfide poisoning in rubber workers

Recently the picture has changed markedly and there are now a number of American publications on the clinical and biochemical action of this poison on viscose rayon workers and on experimental animals The most important of these are contained in a series of studies clinical anatomical and experimental conducted by a group of members of the faculty of the University of Pennsylvania Medical School under the leadership of F H Lewey[3,4,5] These are based on an examination of 120 men employed at the time in those processes of rayon manufacture which involve exposure to fumes of carbon disulfide and on experimental intoxication of animals[4] Mild forms of poisoning were found in nearly 60 per cent of spinners whose exposure is not high while in churners whose exposure is much higher, severe poisoning was found in 20 per cent in one plant in 44 per cent in the other

Clinical

Lewey and his colleagues[3,4,5] found that chronic carbon disulfide intoxication may involve all parts of the central and peripheral nervous systems beginning with psychic symptoms later peripheral neuropathy and damage to the cranial nerves decrease of corneal and pupillary reflexes as well as pyramidal and extra pyramidal signs Varying degrees of parkinsonism were observed also All these had been described already in the foreign literature especially by Germans and Italians

The commonest form of carbon disulfide poisoning is neuritis which may affect any of the nerves but most commonly involves the nerves of the limbs and certain of the cranial nerves optic auditory Both the motor and the sensory nerve fibers are affected causing abnormal sensations and loss of power For evidence of sensory involvement we must depend on the patient s word but motor nerve injury is revealed by objective tests of known reliability

Usually the trouble begins with a sensation of crawling over the skin formication a tendency for the arms and legs to go to sleep' a sensation of coldness and heaviness and a curious feeling that the hand

and foot belong to someone else Pain is associated with these symptoms and tenderness along the nerve trunk and at the same time tests may show touch pain and temperature sense to be heightened rarely di minished

Sometimes irritative symptoms prevail constant or paroxysmal pain in the distribution of one or several nerves or sometimes generally dif fused During the night pain in the legs may reach an intolerable in tensity Aching muscles cramps and sharp pains shooting up and down the legs may make sleep impossible

Any of the nerves may be affected but those more usually involved are the radial and ulnar in the upper limbs the sciatic and external peroneal in the lower Lewey s[3 4 5] group found that areas supplied by the anterior and lateral cutaneous nerves of the thigh often were the seat of hypersensitivity

These symptoms are followed soon by signs of motor nerve involve ment Lewey s[3 4 5] group found such signs more frequently than those of sensory nerve injury The victims complained of early fatigue grad ually increasing loss of strength and especially difficulty in climbing stairs or walking up hill Weakness in the legs appears earlier and is complained of more frequently than weakness in the arms Some ob servers have found the extensor muscles more severely involved than the flexor others find the reverse to be true Sometimes there is an exaggeration of the deep tendon reflexes biceps triceps patellar Achil les especially in the early stages but more often the reflexes are dimin ished The muscles are weak and as time goes on wasting appears more or less marked according to the severity and duration of the poi soning The chronaxia test which measures the time it takes to pro duce excitation of the nerve muscle apparatus together with the strength of current required to produce it was applied by Lewey s group[3 4 5] In a few individuals it showed an increase of electric irritability but in the majority of cases there was a decrease sometimes very marked

Lewey found evidence of peripheral neuritis in 87 per cent of 120 men exposed to fumes of carbon disulfide The course of carbon di sulfide neuritis is slow slower than that of alcoholic rheumatic or syph ilitic origin Recovery proceeds with extreme slowness and the prog- nosis must be guarded because the atrophy pain paresthesias etc may persist even if the victim quits his job

The most striking and the most disastrous effects of carbon disulfide poisoning are upon the brain The mental symptoms run the gamut

from simple irritability and depression to manic depressive insanity If the basal ganglia are involved, parkinsonian palsy occurs In typical cases the attack of active or violent mental derangement comes on fairly suddenly, but careful questioning of the family and working mates always will bring to light an earlier stage of emotional upset, irritability, depression and complaint of loss of memory During this stage there may be excessive sexual excitation, which soon is followed by loss of libido and even impotence

Even in milder poisoning changes in personality are evident especially in the man's relations with his wife and children, and the victims realize this but are powerless to help it Sleeplessness horrid dreams loss of memory are frequent complaints Disturbances of vision, though rarely of a pronounced character are present often and give valuable aid in the diagnosis Diminution or loss of the corneal reflex is stressed by Teleky, central scotoma for color abnormal color vision loss of visual acuity paralysis of accommodation all have been described

Lewey[3 4 5] and his colleagues made a survey of the changes in the nervous system in man and in experimental animals following carbon disulfide poisoning "A comparison of the two discloses the fact that in the human nervous system one finds scattered changes in the ganglion cells of the cerebral cortex of varying degree depending on the severity of the intoxication, disease of the basal ganglia and peripheral nerves and evidence of vascular involvement, in the experimental animal there are more extensive damage to the cerebral cortex and basal ganglia injury of the Purkinje cells vascular changes minor damage to the spinal cord and involvement of the peripheral nerves"

Ferraro Jervis and Flicker[6] also produced experimental carbon disulfide intoxication in cats They found the most important lesions to be a diffuse vascular involvement of a productive type leading to endarteritis occlusion of the vessel and secondary softening and to diffuse neurocellular changes ranging from chromatolysis to severe degeneration scattered all over the brain and cerebellum but most evident in the corpora quadrigemina the cerebellar and vestibular nuclei

Gordy and Trumper[7] reported in 1940 21 cases of chronic carbon disulfide intoxication in workers in American viscose rayon factories from exposures lasting on an average 10 years Encephalopathic symptoms were seen in 90 per cent subjective eye disturbances in 67 per cent with blurring of the disks in 30 per cent, about 75 per cent had lessened libido 70 per cent various degrees of neuropathy affecting the

limbs and over two thirds had gastrointestinal disorders. In 55 per cent the symptoms indicated localized lesions of the central nervous system including parkinsonism.

Finally Weise[8] has published an extensive investigation of the gastrointestinal diseases of German rayon workers, especially peptic ulcer, to which he was led by observing the large proportion of gastrointestinal cases among rayon and rubber workers in Berlin. Among 100 such cases 66 were from the carbon disulfide departments of rayon factories. Comparing them with other textile workers through sickness insurance records he found that the latter had only an average of 2.1 to 3.2 per cent cases in a year, while the rayon workers average 17.7 per cent. Weise produced marked gastrointestinal injury in animals.

Lewey's[3,4,5] warning that the polyneuritis of carbon disulfide intoxication may be very persistent in some cases in borne out by a 1948 report from Italy. Zeglio[9] made a re-examination of 20 viscose rayon workers who had been receiving compensation during some 4 to 8 years for polyneuritis caused by carbon disulfide. Only 1 had completely recovered, 4 had improved and could work but not at the former job, 5 showed no change and 10 were worse. Another Italian, Vigliani[10] writes that mild cases usually recover in 2 to 3 months, severer ones take 6 to 8 months, but if recovery does not occur in that time it probably never will.

The American Standards Association has established 20 parts per million as the maximum allowable concentration of carbon disulfide.

Prophylaxis

The most important point is prevention of such poisoning. Preventive measures consist primarily of rigid examination of the plants to insure modern, safe equipment and the presence of adequate ventilation. The storage and pipe conveyance of carbon disulfide must be satisfactory, and explosions should be guarded against. Medical examination of those exposed to this hazard should be at intervals not greater than one month. Men should be taught to report the first intimation of any unusual symptoms, and if this solvent is the suspected cause of the complaints the employee should be removed at once from the hazard. The drinking of alcoholic beverages by those apt to be exposed to carbon disulfide should be discouraged.

Treatment

Diet.—To date no adequate or specific treatment for cases of chronic carbon disulfide poisoning is known. It would seem likely in view of the similarity of many of these cases to Korsakoff's syndrome that a diet high in vitamin content with the vitamin B complex as an adjunct would be of value. If vitamin B complex is to be used the dosages should be relatively large, e.g., from 50 to 60 mgm. of thiamine chloride parenterally daily, 200 mgm. of nicotinic acid daily, 1 mgm. of riboflavin 3 times per day, 20 mgm. vitamin B_6 twice daily parenterally and so on. Liver extract in dosages similar to those advised in the chapter on Manganese might be tried.

Psychiatric and Ophthalmological Attention.—The aid of a psychiatrist will be needed for most of these patients since a program of mental hygiene will need to be instituted. The ophthalmologist should be consulted on problems relating to the eyes.

Exercises for existing muscular weakness, sedation and tonics may be of value. If parkinsonian-like symptoms are present, a trial of those drugs mentioned in the section on Mercury for control of these manifestations might be made.

Treatment of Acute Case.—The acute case will be seen rarely. When such a case does occur, artificial respiration, 5 to 7 per cent carbon dioxide in oxygen inhalations and the respiratory and circulatory stimulants mentioned in the sections on Trichlorethylene and Alcohols are to be used.

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HYDROGEN SULFIDE

By Howard W Haggard

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Introduction

Hydrogen sulfide H_2S, is a colorless gas having a molecular weight of 34 08, a specific gravity of 1 192 (air = 1) and a boiling point of −59 6 C It is readily soluble in water kerosene and crude oil In low concentrations it has the familiar odor which the gas itself imparts to rotten eggs This odor is readily recognizable in concentrations of the gas in air as low as 0 34 parts per million (0 000034 per cent) In moderately high concentrations the characteristics of the odor change and the gas has only a sweetish or occasionally acid odor The sense of smell is unreliable and treacherous in the detection of hydrogen sulfide not only because of the change in the character of the odor but also because the olfactory nerve endings are paralyzed by the gas The sense of smell is lost after 2 to 15 minutes exposure to concentrations of 100 to 150 parts per million (0 010 to 0 015 per cent)[1] A qualitative and roughly quantitative test for the presence of hydrogen sulfide is made by exposing moist lead acetate paper to the air suspected of contamination At a concentration of 0 34 parts per million (0 000034 per cent) the paper darkens after about 30 seconds at a concentration of 3 4 parts per million (0 0034 per cent) after 2 seconds and at a con

centration of 34 parts per million (0 0034 per cent) and over it darkens immediately[2] The concentration may be determined quantitatively by various methods of which the two most common depend upon the reaction between hydrogen sulfide and iodine in solution with the formation of hydroidic acid and sulfur and corresponding loss of iodine which can be estimated by titration and the reaction between hydrogen sulfide and bromine in water solution with the formation of sulfate which can be estimated gravometrically as barium sulfate[1] In obtaining samples of air suspected of containing hydrogen sulfide care must be taken that the container used is dry since the gas will dissolve in any moisture present

Sources of Exposure

Hydrogen sulfide may occur in the gas of volcanoes in certain natural waters in mines as stink damp from the decomposition of pyrites and in petroleum oil containing a high percentage of sulfur from which it is given off during refining It is formed whenever protein containing material putrefies and hence may occur about tanneries in the washwater from sugar beets during the manufacture of glue and especially in sewer gas The gas has little use in the chemical industry but is a by product of many processes in which sulfur or sulfur containing materials are employed as in the manufacture of coke rubber sulfur dyes rayon when the viscose process is used and soda when the LeBlanc process is used Water and petroleum products may absorb considerable amounts of hydrogen sulfide which can be given off later to the development of dangerous concentrations in the air The main direct use of hydrogen sulfide is as a reagent in the chemical analysis for heavy metals For this purpose it may be generated as needed or obtained from tanks of the compressed gas Bursting or leaking of these tanks has been responsible for serious acute poisoning

Action of Hydrogen Sulfide

Hydrogen sulfide is a systemic poison with a toxicity little less than that of cyanide and also an irritant to the respiratory tract and especially to the eyes on which its action is characteristic

Irritation

The irritant action of hydrogen sulfide does not arise from the gas after absorption but is due to direct action on the moist surfaces. For most irritant gases, such as acid fumes and sulfur dioxide, except in extremely high concentrations there is no demonstrable lesion such as corrosion attributable to the direct action of the gas[3]. The irritant disturbs the biochemical processes of the cells and this insult is followed by the inflammation which shows no distinguishing characteristics except as to areas affected and intensity. Hydrogen sulfide, on the contrary, may produce in addition to or even in the absence of general inflammation a characteristic lesion of the cornea[4,5,9]. It is possible that this lesion is due to the sulfide ion which may be kerolytic[3]. Depending upon the concentration of hydrogen sulfide and the duration of exposure the effects on the eye may be predominantly those of conjunctivitis or of corneal injury, and frequently both occur. The corneal lesion may consist of scaling or vesication followed by pitted erosions which in severe cases may become confluent and in which the epithelial layers are loosened. The main symptoms in mild injury may consist of foggy vision and such phenomena as color rings about lights which may be due to interference phenomena. Corneal injury may be slight and the main symptoms be those of an extremely painful conjunctivitis with lachrymation and marked photophobia. In the mildest degree of inflammation there is a persistent sensation as of grains of sand in the conjunctiva. Inflammation of the eyes may result from prolonged exposure to concentrations of hydrogen sulfide which do not cause any evident inflammation of the respiratory tract.

The inflammation of the respiratory tract resulting from hydrogen sulfide shows no characteristic symptomatology[3]. In moderate exposure the inflammation is mainly of the upper respiratory tract, in severe exposure it may extend deeper and lead in occasional instances to bronchopneumonia[8,7,10]. Death from hydrogen sulfide occurring several hours to several days after exposure is due to the involvement of the respiratory tract.

Systemic Poisoning

Hydrogen sulfide can be absorbed from the respiratory tract but is in oxygenated blood and also in liver tissue rapidly oxidized to harmless sulfates[11,1]. The systemic effects are due to the action of the un

oxidized gas upon the nervous system[3, 11, 12] but it is not known whether this action is directly or indirectly through disturbance of an enzyme system On cessation of exposure to the gas the action is quickly terminated because of the rapid disappearance of the absorbed gas[11, 12]

It was formerly believed but incorrectly so that hydrogen sulfide exercised its action as an asphyxiant by combining with hemoglobin to form sulfhemoglobin which is incapable of carrying oxygen[11, 15] Under this conception hydrogen sulfide was assumed to act much like carbon monoxide The symptomatology is however distinctly different from that of carbon monoxide particularly so in the immediate and violent effects from high concentrations which cause respiratory paralysis Furthermore sulfhemoglobin is not found in sufficient amounts in the blood after poisoning to cause asphyxiation or indeed under ordinary conditions to be pathognomonic of poisoning by this gas Hydrogen sulfide does not react with oxyhemoglobin but does react readily with methemoglobin and hence the appearance of sulfmethemoglobin as a normal post mortem phenomenon particularly in the blood in the vessels about the abdominal viscera Sulfmethemoglobin may appear in the blood of living healthy individuals not exposed to hydrogen sulfide in the air and may be presumed to arise from the conversion of methemoglobin normally present to the sulfur compound possibly from hydrogen sulfide occurring in the alimentary tract

Hydrogen sulfide in small amounts depresses the nervous system in large amounts it stimulates and in very large amounts it paralyzes[11] The effects dangerous to life are those exercised upon the nervous control of respiration Death in acute poisoning results from failure of respiration and consequent asphyxia The respiratory failure is occasioned through two separate processes depending upon the concentration of the gas inhaled Moderately high concentrations may cause hyperpnea by stimulation The excessive breathing results in apnea vera If removal from the gas is possible before severe asphyxia has developed from the respiratory failure breathing may be reestablished spontaneously Very high concentrations cause immediate respiratory paralysis and breathing does not become reestablished spontaneously If removal from the gas is possible within a very short time life may be sustained by artificial respiration and normal respiration restored after the oxidation of the absorbed hydrogen sulfide

The symptoms of acute hydrogen sulfide develop rapidly on exposure to the gas but because of the rapid oxidation of hydrogen sulfide in

the body, they pass off quickly when inhalation of the gas ceases The gas is to a high degree a non accumulative poison, if its victims are revived there are no important systemic sequelae although symptoms from irritation of the respiratory tract may develop Death in acute poisoning is as rapid as from cyanide poisoning Less severe poisoning may be marked by convulsions and dyspnea In subacute or chronic poisoning[11] from daily exposures to the gas the main symptoms, in addition to those of irritation are mild depression, headache malaise and possibly, mild gastrointestinal disturbances with loss of appetite These symptoms ordinarily clear up rapidly when the exposure is terminated

Knowledge of the *pathological changes* resulting from fatal poisoning is limited In acute poisoning with rapid death no changes may be found post-mortem, in death occurring some hours or days after exposure the changes are limited to the respiratory tract and are those of edema or bronchopneumonia In animals exposed to subacute poisoning it is reported that the liver kidneys and spleen may show deposits of hemosiderin which in the liver are mainly located in Kupffer s cells which also show signs of degeneration and necrosis[7] These findings have not been reported for man In rapid fatalities in man the odor of hydrogen sulfide in the tissues has been reported post mortem but in this respect caution must be exercised for the gas is a normal development of decomposition

There is some controversy over the possible absorption of hydrogen sulfide through the skin instances of such poisoning have been reported from the use of sulfur ointments It would appear from animal experiments that such poisoning is improbable since absorption is too slow to cause systemic effects[7] Ammonium sulfide applied to the skin may be absorbed particularly in the presence of abrasions the symptoms from alkaline sulfide are identical with those from inhalation of hydrogen sulfide but apparently with greater formation of sulfmethemoglobin[17] Hydrogen sulfide applied locally to the skin in concentrations far higher than those which can be inhaled without immediate fatality may result in some absorption and also discoloration of the skin Cutaneous absorption however plays an unimportant part in poisoning from exposure to air contaminated with hydrogen sulfide or from contact with solutions of the gas exposed to the air as in partial immersion in water containing hydrogen sulfide The dangers from hydrogen sulfide other than those resulting from irritation of the eyes come from inhalation of the gas

In *standards for industrial safety* the maximum permissible concentration of hydrogen sulfide in air is at present accepted as 20 parts per million (0 002 per cent) for an exposure not to exceed 8 hours Some irritation of the eyes has been reported for concentrations as low as 15 parts per million (0 0015 per cent) for 8 hours[19] No systemic effects may be expected from prolonged exposure to concentrations of the order of 30 to 50 parts per million (0 003 to 0 005 per cent) Exposure to 500 to 700 parts per million (0 05 to 0 07 per cent) may endanger life in 30 minutes to 1 hour and exposure to concentrations of the order of 5 000 parts per million (0 5 per cent) may cause immediate death[3 9]

Treatment of Poisoning

The victim of poisoning should be removed to fresh air as quickly as possible and kept warm If respiration has stopped or is failing artificial respiration should be applied but with caution and for no longer than necessary because of the possible congestion of the lungs

Injury to the eye may be treated by instillation of 1 drop of bland oil which is said to assist in alleviating the pain administration of 3 to 4 drops of 1 1 000 solution of epinephrin at frequent intervals may prove helpful and if the pain becomes severe local anesthesia and hot or cold compresses may be beneficial

The irritation of the respiratory tract should be treated symptomatically

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XXXI

IONIZING RADIATION

By Alice Hamilton and Rutherford T. Johnstone

Revised by Harriet L. Hardy

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Introduction

The use of ionizing radiation in industry is recent and as yet not extensive. The accidental exposure of workers to radiation in mining radioactive ores is much older, but the discovery of the part played by emanations of radium in the sickness and death of these miners was made only lately. Even now the industrial uses of radiation are few, but the injuries that have resulted in some cases have been so spectacular as to arouse wide public attention and lead to strenuous efforts of control, much as the occurrence of "phossy jaw" in a relatively small proportion of match makers led to a world wide campaign against the use of white phosphorus.

The development of atomic energy coincidental with its military use has led to many new worker exposure problems as yet not described. Industrial, agricultural, and medical research workers are now able to use isotopes produced by the cyclotron and the several piles located at

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troduced x ray hazard to the public is the device sold to shoe stores to demonstrate that a shoe does or not fit[36] There may be x ray burns to the tissues of the foot and interference with normal bone growth from this source[37]

In industrial use there is far more risk of minor injuries of x ray lesions of the skin since the precautions are likely to be far from perfect but it is doubtful if there will be cases of such severity as have occurred among radiologists for the workman has not so strong a motive to keep on at work after he has discovered that it is dangerous So far the only instances of strictly industrial x ray lesions that have come to light are skin lesions of more or less severe character These which usually are on the fingers are intensely painful even when quite insignificant in appearance and are very obstinate As we know from non industrial cases such lesions may undergo cancerous change years later (Porter)[60] but as yet no cases of that sort have been reported from industry

Hunter and Robbins[4] after careful study have described safe practice for personnel associated with diagnostic and therapeutic radiation In addition to adequately shielded equipment individuals exposed to new equipment or new tasks involving x ray exposure should wear film badges to determine the level of ionizing radiation received Such film badges should be provided developed and read by qualified individuals usually to be found in governmental agencies such as the Bureau of Standards or in state labor or public health departments Such film badge readings should be supplemented by a careful medical examination and complete blood counts at least three to be taken at weekly intervals before exposure to get baseline values and thereafter at monthly to semi annual intervals depending on the degree of exposure Reference is here given to detailed information on proper protection against the dangers involved in the use of x rays[9 1 3 6 31]

Radium

This section is based largely on the studies of J C Aub and associates[5] and R D Evans According to Evans [5] records show that several hundred people were killed through various types of radium exposure prior to 1930 Since then the number of persons engaged in the industrial handling and application of radium has increased about fifty fold Radium is formed by the natural radioactive decay of its ultimate parent

present at Oak Ridge, Brookhaven and Chicago. The betatron, a machine for generating powerful x-rays, is being made for industrial inspection of steel. Kerst[18] describes its use in treating malignancies and betatrons for hospitals are now in construction. Since 22 million electron volts of energy or more are involved, and it is known that neutrons are also emitted, the protection of technicians will be a problem.

Roentgen Rays

Roentgen rays may be used industrially either for radiography or for fluoroscopy but the latter is much better adapted for such purposes and is almost always used. The strength of the rays varies according to the thickness of the material to be penetrated: soft rays will do to show the position of the metal plate in rubber heels, hard rays must be used to reveal flaws in castings. Undoubtedly the chief source of x-ray injury is still the use of these rays in medical practice although now the proper measures for protection are so well known that instances of serious injury are rare.

Some students of the genetic effects of ionizing radiation question the wide and repeated use of x-rays in diagnostic work in such a large proportion of the public. Because fetal tissue is more sensitive to ionizing radiation than adult there must be careful control of the number of x-ray studies taken of pregnant women. As pointed out by Daland[7] recently, surgeons are not sufficiently alert to the danger of prolonged manipulation of fractures under the fluoroscope, a practice which is dangerous to patient and helping attendant as well as the manipulator. It is well to know that a gastrointestinal study by x-ray gives the patient about 30 r while a routine chest x-ray may give as much as 3 r. Reasonably well substantiated reports of yearly check up of normal children's bony growth by fluoroscopic study are mentioned to condemn this practice. That growing bone is more vulnerable than adult to x-rays is well established. It is important from knowledge of the effect of ionizing radiation and from clinical reports of injury for any physician using fluoroscopy to scrupulously guard himself against the use of excessive time milliamperage and to control portal size with a view to keeping down the dose of x-rays delivered. The fate of the radiologist in this type of work for which adequate protection has not been devised is important. Recent papers on the high incidence of leukemia in radiologists is definite evidence that this is hazardous work.[9, 8] A recently in

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military instruments Consequently a number of dial painting concerns have both fluorescent and radium painting going on in different parts of the same plant In safeguarding the health of the radium painters this fluorescent painting is a most fortunate circumstance because it provides a simple means of rotating personnel between radium and non radium work

A modern industrial use of radium is found in the static eliminator The ionization effect of the alpha particles from decaying radium acts to dissipate static electricity in textile and paper mills More serious industrial exposure to radioactive substances occurs in mining radioactive ores handling and testing the products of the ores making up radon seeds and making and applying luminous paint to the figures on timepieces and to parts of apparatus Such exposure has resulted in pulmonary carcinoma necrosis of bone malignant growth of the bone and primary blood diseases of various kinds Carcinoma of the lungs is the kind seen in miners of the Schneeberg region of Saxon Switzerland where the cobalt arsenide ores are radioactive and for more than a century it has been known that a large proportion of the miners died prematurely of lung disease with wasting The discovery that the disease was pulmonary carcinoma was made in 1878 confirmed in 1913 and again in 19 6 At first the arsenic in the ore was supposed to be the carcinogenic agent but the later studies attributed this action to the radioactivity of the ore The same ore is found on the Bohemian side of the mountain and pitchblende is now mined there Here also the miners suffer from pulmonary carcinoma [5,63] Robley Evans of Boston suggests that the majority of the malignant lesions are in the large bronchi because of the anatomical characteristics of the upper respiratory tract and accessibility to radiation effect

In September 19 4 Theodore Blum a dentist[4] described before the American Dental Association a form of necrosis of the jaw with severe buccal infection in dial painters applying a luminous paint and he attributed it not to phosphorus but to the radioactive substances in the paint He was the first to discover the real cause of this affection which had attracted the attention of other dentists in northeastern New Jersey but had been diagnosed as phossy jaw or Vincent s angina or syphilis In some of these cases there was evidence also of a profound injury to the blood forming tissues

The cases of radium necrosis and aplastic anemia among these women dial painters attracted widespread interest and much controversy from which however a clear picture gradually emerged[18] The

uranium which occurs in commercial quantities in a few isolated mineral deposits Radium is the fifth in a long series of decay products of uranium

In its radioactive disintegration radium emits alpha rays For practical purposes the alpha ray can be thought of as an energetic atomic bullet whose range is about 50 microns in living tissue and capable of doing lethal damage to most of the cells traversed along its path After the radioactive decay of radium by its emission of an alpha ray the residual is an atom of radon Radon is the heaviest member of the group of noble gases helium argon etc and is therefore chemically inert However physically radon like radium is radioactive and emits alpha rays in its disintegration Each decaying atom of radon experiences seven subsequent radioactive transformations before finally becoming a stable atom of lead In the commercial use of radium radioactive equilibrium usually is present then each of the decay products radon radium A radium B radium C and radium C′, has the same rate of radioactive emission as radium

The alpha radioactivity of radium in equilibrium with its decay products therefore is four times as great as the alpha radioactivity of radium element alone From the standpoint of toxicity, that is cell damage produced by alpha rays the decay products of radium are three times more hazardous than radium itself All salts of radium have the same toxicity as the elemental radium which they contain

In the preparation of self-luminous compound a small amount of mesothorium and some radium salt usually radium chloride or radium bromide is mixed with a binding agent and specially prepared and finely powdered zinc sulphide crystals The alpha rays emitted by radium and mesothorium and their decay products bombard the zinc sulphide crystals and cause them to emit visible light in tiny flashes one for each alpha ray The integrated effect of thousands of such tiny flashes of light per second is that of a uniform emission of light The presence of mesothorium of shorter radioactive half life in the self luminous mixture is currently under study by Evans and Hempelmann[10] as possible explanation for the timing of the fatalities among the industrial workers This in contrast to patients who received radium as therapy for arthritis and other diseases and survived much longer periods

Zinc sulfide emits a visible light when irradiated by ultra violet light For this reason a mixture of zinc sulfide and binder is used also as a fluorescent paint without the addition of any radium to the mixture This fluorescent paint is applied to a number of the markings of modern

no deviation from a normal blood count and tissue abnormalities are mild or absent

Because of the wide variations in body resistances some patients with only micrograms of radium may be more quickly and more seriously affected than others containing as much as 20 micrograms of radium Measurements by J C Aub and R D Evans now include 7 human cases in which more than 0 0 micrograms and less than 0 5 micrograms of radium have been carried for some 7 to 25 years without the appearance of any clinical symptoms of chronic radium poisoning On the other hand several unpublished cases seen by these workers and others measured by Martland with the same or similar analytical apparatus have resulted fatally when the radium burden was between 1 2 and micrograms of radium

Based on these observations a committee called together in 1941 by the National Bureau of Standards tentatively established 0 1 micrograms of radium fixed in the body as the tolerance value for man This figure replaces tolerance values of 10 micrograms and 1 microgram recommended by individual observers a number of years ago before adequate physical methods were available for detecting smaller quantities of radium in living persons

Evans of Boston has taken advantage of the fact that when radium is deposited in the body radon a decay product of radium can be measured in the expired air This procedure is now in general use in industries handling radium Evans gives the figure of 10^{-1} curie per liter as the safe amount of radon in exhaled air

Prophylaxis and Treatment —Radium poisoning need never occur if proper precautions are taken but these precautions must be carried out meticulously since radium enters the body with considerable ease Necrosis of the bones anemia and buccal lesions were noted in dial workers in the 19 4 1925 outbreak of this disease It was felt at that time that the radium entered the body through ingestion since these workers were accustomed to point their brushes with their mouths Today radium workers are cognizant of this danger and avoid acts which might lead to ingestion of this substance Prevention is directed today against the inhalation of the dust which primarily imposes the obligation of correct hygiene upon plant management

In general there are two groups of workers in radium dial manufacture who must be protected The first of these are the painters usually young women These should be provided with individual glass hoods within which the operation is performed The glass protects the

chief credit must be given to Martland who not only published the first description of the pathology of this new occupational disease[60] but followed year after year the fate of the women who had been exposed to the luminous paint and thus discovered the later manifestations of this kind of radium poisoning In the early cases which developed fairly rapidly there was a rarefying osteitis of the bones of the jaw with sepsis and anemia usually of the aplastic type[6] In cases developing later there was necrosis of other bones the femur and the humerus (Martland)[61] the cranial bones (Flinn and Seidlin)[33] Still later, in 1931 Martland and Humphries reported[6] 5 instances of osteogenic sarcoma among 18 victims of fatal radium poisoning in New Jersey and Connecticut which would make 27 per cent while the incidence of osteogenic sarcoma in the general population is only 0 07 per cent Three former dial painters still living at that time had bone lesions which were very suspicious of neoplasm

Silverstone[9] says that the actual dose required to produce radioactive cancer is not known but it is known that for its production there must be either a long continuous exposure or many intermittent exposures He does not believe that the radio necrotic tissue becomes cancerous but cancer may arise in the viable tissue nearby where degenerative and regenerative changes continue side by side Both are progressive even after the radioactive agent is withdrawn The type of neoplasm depends not on the nature of the injurious agent but on the type of tissue affected The neoplasm arises in the irradiated tissue but once established it behaves like any other of similar structure and anatomical site

As for the blood changes the history of radium poisoning in some of the famous radiologists had shown that such changes might be very varied in character Martland[1] saw in addition to cases of typical aplastic anemia 5 of leucopenic anemia of the regenerative type and von Jagic and associates[11] reported 3 cases of lymphatic leucemia, Carman and Miller one[1]

When taken into the body radium behaves biochemically like calcium A portion of the ingested radium eventually is deposited in the bones The alpha rays from radium and from its decay products which build up in the bones bombard the blood producing centers the bone building cells osteoclasts and osteoblasts and the bone structure

In chronic radium poisoning where the body contains 1 to 10 micrograms of radium fixed in the skeleton there are usually no clinical symptoms until some 5 to 15 years after the exposure There is often

no deviation from a normal blood count and tissue abnormalities are mild or absent

Because of the wide variations in body resistances some patients with only micrograms of radium may be more quickly and more seriously affected than others containing as much as 20 micrograms of radium Measurements by J C Aub and R D Evans now include 7 human cases in which more than 0 0 micrograms and less than 0 5 micrograms of radium have been carried for some 7 to 25 years without the appearance of any clinical symptoms of chronic radium poisoning On the other hand several unpublished cases seen by these workers and others measured by Martland with the same or similar analytical apparatus have resulted fatally when the radium burden was between 1 2 and micrograms of radium

Based on these observations a committee called together in 1941 by the National Bureau of Standards tentatively established 0 1 micrograms of radium fixed in the body as the tolerance value for man This figure replaces tolerance values of 10 micrograms and 1 microgram recommended by individual observers a number of years ago before adequate physical methods were available for detecting smaller quantities of radium in living persons

Evans of Boston has taken advantage of the fact that when radium is deposited in the body radon a decay product of radium can be measured in the expired air This procedure is now in general use in industries handling radium Evans gives the figure of 10^{-1} curie per liter as the safe amount of radon in exhaled air

Prophylaxis and Treatment—Radium poisoning need never occur if proper precautions are taken but these precautions must be carried out meticulously since radium enters the body with considerable ease Necrosis of the bones anemia and buccal lesions were noted in dial workers in the 19 4 1925 outbreak of this disease It was felt at that time that the radium entered the body through ingestion since these workers were accustomed to point their brushes with their mouths Today radium workers are cognizant of this danger and avoid acts which might lead to ingestion of this substance Prevention is directed today against the inhalation of the dust which primarily imposes the obligation of correct hygiene upon plant management

In general there are two groups of workers in radium dial manufacture who must be protected The first of these are the painters usually young women These should be provided with individual glass hoods within which the operation is performed The glass protects the

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In order to make certain that the worker is not absorbing too much radium two routine procedures are in order One of these is to do a complete blood count once a month The other is to have the worker undergo breath radon measurements The reader is referred again to the article by Evans for details of this measurement

In the further prevention of radium absorption it is felt that an adequate intake of calcium is of value This is based upon belief that radium metabolism closely parallels that of calcium On the other hand if a worker reveals the presence within the body of excessive radium then excretion of radium is aided by a low calcium intake[5]

In chronic radium poisoning a regime directed towards aiding in the excretion of radium should be followed It is suggested that a low calcium diet parathyroid extract and large doses of ammonium chloride be instituted That such treatment will have much effect is to be questioned Treatment of any existing anemia is also advisable

Thorium

Thorium naturally radioactive is used in industry to make gas mantles as a catalytic agent and in ceramics To date there have been no reported ill effects from industrial use of this element although pulmonary carcinoma is considered a possibility by Evans and Goodman in their report in 1940[9] Thorium dioxide is sold in a collodial suspension under the trade name of thorotrast for use intravenously in humans as a diagnostic tool This is probably not a safe procedure Damage to liver spleen and lymph nodes has been reported thoron the decay product of thorium has been found in the expired air of patients so treated MacMahon reported sarcoma of the liver in a patient given thorotrast[7]

Uranium

In the past uranium has been used in small amounts in the ceramic and glass industries and in steel manufacture This radioactive element is of basic use *in atomic energy development* Since there are not unlimited supplies only workers in government projects have been exposed to uranium From past experience (Leconte[32] deLaet)[19] and from animal studies (MacNidel[4] Hodge and associates)[41] it is known that the soluble

worker's face, especially the breathing zone yet enables a clear vision of the working field The booth should be exhausted by suction ventilation[36] The head should be covered the clothing simple and no personal articles such as cosmetics cigarettes candy or food permitted within the radium room

Rigid personal hygiene must be enforced under supervision and not left to the individual's inclination An excellent regime has been suggested by Evans[6] as follows

The hands must be thoroughly cleaned always before eating or smoking To remove radium paint from the hands Dr George L Morris has tested a number of solvents He has found most effective and least toxic a mixture of 1 part xylene 1 part trichlorethylene and 2 parts ethyl alcohol This mixture should be rubbed onto the dry skin and removed before it evaporates with soap and water The skin then is thoroughly dried and examined in a darkened room under ultra violet light which will reveal any residual luminescent material If the first cleaning is not complete as is often the case the entire solvent and washing process is repeated until the ultra violet lamp reveals no residual radium paint In the dark room many of the new ultra violet lamp bulbs will be found satisfactory For example, the GE 4 watt RP-12 360 BL lamp can be obtained in a convenient fixture (Grimes Mfg Co Urbana Ohio) including a filter for removing visible light If a more powerful but less portable source is desired the GE type BH4 (sunlamp with filter to remove visible light) may be installed These new lamps are more suitable than the argon glow lamp because the latter gives more visible light and less ultra violet radiation

'One wash basin with solvent soap hot and cold water and paper towels should be provided for every five workers A waste receptacle with a swinging lid operated by a foot pedal should be provided for used towels In very large plants one wash basin per ten to fifteen active workers may suffice especially if rest periods and lunch hours are staggered The washing and dark room areas are most useful if adjacent to one another Local ventilation should be provided in both areas to remove solvent fumes

A separate sink should be provided for the disposal of contaminated solvents which have been used to wash radium compound from imperfect or discarded work

The other group involved in the radium room is that composed of inspectors foreman and those who clean the room These are exposed likewise to the dust and need just as careful supervision in hygiene

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Thorium

Thorium, naturally radioactive, is used in industry to make gas mantles, as a catalytic agent and in ceramics. To date there have been no reported ill effects from industrial use of this element, although pulmonary carcinoma is considered a possibility by Evans and Goodman in their report in 1940[9]. Thorium dioxide is sold in a colloidal suspension *under the trade name of "thorotrast"* for use intravenously in humans as a diagnostic tool. This is probably not a safe procedure. Damage to liver, spleen and lymph nodes has been reported; thoron, the decay product of thorium, has been found in the expired air of patients so treated. MacMahon reported sarcoma of the liver in a patient given thorotrast.

Uranium

In the past uranium has been used in small amounts in the ceramic and glass industries and in steel manufacture. This radioactive element is of basic use in atomic energy development. Since there are not unlimited supplies only workers in government projects have been exposed to uranium. From past experience (Leconte[52], deLaet)[49] and from animal studies (MacNidel, Hodge and associates)[47] it is known that the soluble

salts are responsible for uranium poisoning and the chief lesions are to be found in the kidney It must be pointed out that the toxic effects of uranium in experimental animals[11] and as far as reported in man are due to the chemical action of this heavy element Natural uranium consists of over 99 per cent uranium of atomic weight (mass number) of 238 with a half life of 4.51 × 10^{9} year The isotopes U^{3} and U^{4} are present in only a total of 718 per cent but due to their shorter half life (7.07 × 10^{8} year and 2.35 × 10 year respectively) are capable of severe biological damage[4] When separated in atomic energy development U[235] is handled with great care Due to its slow rate of radioactive decay uranium[238] does not as far as is known produce radiation damage Workers at the Los Alamos Scientific Laboratory exposed to varying amounts of insoluble uranium compounds over a period of three years of medical supervision have shown no changes in urinalysis or blood count nor has there been any correlated illness

To date there have been no reports of symptoms in workers exposed to uranium in any form Hodge and associates believe that only hexavalent uranium can be absorbed into the blood All observers agree that the chief lesions of experimental uranium poisoning take place in the kidney Willis and Main[6] working with animals discovered that the bicarbonate more than citrate or lactate ion diminished the renal fixation of hexavalent uranium These experimental studies may have some bearing on the treatment of uranium poisoning should it occur

Plutonium

Government workers have been exposed in atomic energy development to controlled quantities of plutonium A great deal is known of the behavior of this material in the body through animal study[18] Plutonium is a bone seeker as are many of the radioactive fission products and can be shown to shorten the animals' life span[3] Some of the radioactive materials now available have shown carcinogenic properties in laboratory studies after varying periods of time depending on the proximity of the ionizing radiation to tissue Langham at the Los Alamos Scientific Laboratory [63] has been able to establish methods for study of excreta for accurate estimate of plutonium excretion in human workers These studies correlate with exposure The values obtained are used to calculate as in the case of radium how much plutonium

is in the skeleton and hence the safe level beyond which the worker is removed from further exposure 6 microgram of plutonium has been set as the safe level

Workers who demonstrate by urinary studies that a certain amount of plutonium is fixed in the skeleton are permanently removed from exposure to that material Schubert[77, 8] of the Argonne Laboratory in Chicago has done work with plutonium poisoned animals in an attempt to develop a method of treatment He finds that zirconium a harmless material will displace plutonium in the bony skeleton Then by giving citrate the plutonium is excreted as a harmless complex Schubert has been able to demonstrate a definite displacement of the plutonium up to 30% Because of the fact that plutonium deposited in the bone emits an energetic locally acting alpha particle and is a material of long half life the treatment outlined by Schubert would probably not prove adequate if a laboratory accident resulted in body deposition of much plutonium above the amounts suggested as safe Because of the long radioactive life of plutonium this is not yet a clinically useful form of treatment

Isotopes

There are more than 600 radioactive isotopes now known Many of these are made in cyclotrons The Oak Ridge and Brookhaven piles now are producing isotopes and supplying certain of them to qualified research centers The 1948 report of the Atomic Energy Commission to Congress lists over 1 000 studies with isotopes in 136 institutions covering industrial agricultural and medical problems The isotope I^{131} giving out gamma rays has been used for some years now for diagnostic and therapeutic handling of thyroid disease P^{32} which emits beta particles has been used to manage certain malignancies and polycythemia with varying degrees of success reported Co^{60} has sufficient penetrating energy and has become cheaper annually so that it is now competing successfully with radium in treating pelvic malignancies C^{14} and more recently H^{3} are proving of great value in studying basic cellular physiology and metabolic processes Radioisotopes of manganese iron copper sodium zinc arsenic antimony gold bromine potassium calcium strontium sulfur and gallium have been used to study problems of medical interest The behavior of trace metals in the body and iron metabolism have been and are being investigated[8, 60] Workers in these

projects are protected by clothing, shielding and, when necessary, by study of excreta[c] Depending on the life of the isotope and the kind of energy emitted proper health monitoring , as it is called, provides knowledge of how much radiation the worker receives

Biological Effects

Reference is made to sources of information on this complex subject which is at present far from completely understood[11 1 51 56 0 74 81] The problem the physician must grasp is that biological effects vary enormously depending on the kind of ionizing radiation and the quantity reaching body tissue In addition, there is great variation in the susceptibility of different cells in the body to the effect of ionizing radiation[8 4] An additional problem is the delay in clinically detectable disease following all except overwhelmingly large doses such as resulted from weapons Briefly the biological effects of various kinds of ionizing radiation are

(1) Alpha particles penetrate only about 50 microns of tissue but have great intensity of ionization and if taken into the body do lethal damage to the cells in proximity

(2) Beta rays are high speed electrons They are stopped by a few millimeters of most materials Because of intense local ionization the unprotected skin usually is in greatest danger from beta effect

(3) Gamma rays are electromagnetic radiation of short wave length as are roentgen rays though from different sources Neutrons are uncharged fundamental nuclear particles emitted at varying speeds when certain elements are bombarded These three forms of energy are grouped together because their biological effectiveness depends on their power to penetrate the body producing tissue damage as they pass The end result in sufficiently large doses as is well known will be malignancy depending in location on the tissue receiving the ionizing effect and varying with tissue susceptibility (see Desjardins and Williams) or in the case of whole body effect aplastic anemia due to bone marrow depression For help in grasping the significance and importance of the varying magnitudes of radiation exposure in day by day activity work diagnosis and therapy and possible military emergency Evans and Williams have prepared the chart below Careful study of the relative dosages recorded here will clear common mis

RADIATION EXPOSURES
AND
BIOLOGIC EFFECTS
I

COSMIC RAYS AT SEA LEVEL ~ (0 0001 r/day)
K[40] IN HUMAN RED CELLS ~ (0 0001 r/d y)
TERRESTRIAL GAMMA RAYS ~ (0 0001 r)
RADIUM IN NORMAL SKELETON ~ (0 0003 to 0 003 r/day)
CROOKS LENS (01 r/8 hours (on eyes))
ANTI THEFT FLUOROSCOPY ~ (0 1 r) (Whole body)
CHEST X RAY PHOTOFLUOROGRAPHY ~ (1 r)
FEUZAL LENS (0 05 r/8 hrs) (on eyes)
PELVIMETRY ~ (1 r/film)
Ra WRIST WATCH ~ (0 1 r/day)
SHOE FITTING FLUOROSCOPE (1 0 to >100 r/fitting)
CHEST X RAY (14 × 17 film) 0 05 ~ 1
DENTAL X RAY (4 to 5 r/film)

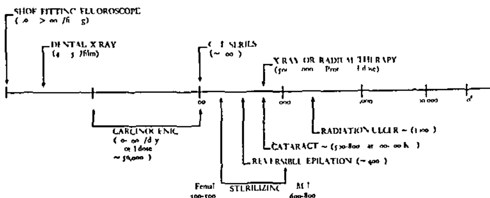
0 0001 Roentgens | 0 001 | 0 01 | 0 1 | 1 | 10

NO DETECTABLE BIOLOGIC EFFECTS ?
ACUTE OR CHRONIC

Chart designed by
Evans, R D and Williams, C. R.†
Adapted by Lewis, S October 1953
~ pproximate
† To be published.

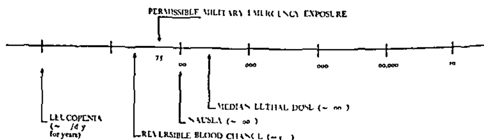
RADIATION EXPOSURES
AND
BIOLOGIC EFFECTS
II

Local Effect



RADIATION EXPOSURES
AND
BIOLOGIC EFFECTS
III

Whole Body Eff



NOTE – ADDITIVE EFFECTS

LIFE SPAN ~ pe oo
WHOLE BODY

GENE MUTATIONS ~ 5 oo
TO DOUBLE SPONTANEOUS RATE PER GENERATION.

conceptions It also should point up the potential dangers of excess and repeated diagnostic x ray study of the population

The current problem of evaluating low dose radiation effect is a difficult matter and now unsettled Government workers and research workers using isotopes are because of the known inherent dangers receiving great protection Film badges and pocket ionization chambers control weekly exposure to the level of 0 3r the present permissible dose Reference is made to discussion of present health monitoring methods of control of the amount of ionizing radiation in the workers environment [81 1 6 7] The table below indicates the present standards of human radiation exposure This was prepared in September 1951 by Levin the Massachusetts Institute of Technology Radiological Safety Officer for use in that institution

Currently Accepted Values r1

A Doses producing biological effects
B Maximum permissible doses
C Emergency doses

A *Doses producing biological effects*

1 600 roentgens whole body short time exposure will kill ~ 100 %
350 450 r whole body short time exposure will kill ~ 50

2 50 r whole body short time exposure will temporarily depress white cell count in ~ 50 of cases

(Note short time exposure is assumed to be in the order of one day or less)

3 Sterilization

Male 300-600r } ~ 60 of these cases will be of temporary sterility
Female 300-350r }

4 Skin Erythema Dose (S E D) for short time exposure

10 KV X Rays	100 r
100 KV	350 r
200 KV	600 r
1000 KV	1000 r
Radium gamma rays	1000 r
p[32] Beta rays	200 rep (roentgens equivalent physical)

B *Maximum permissible exposure*

1 *Whole body exposure* (for 8 hours/day 5 days/week)

a X ray and Gamma radiation (up to 3 Mev)
0 3 r/week to blood forming organs which are assumed to be at a depth of 5 cm below the surface This dose corresponds to 0 5 r/week measured at the surface of the body or to 0 3 r/week measured in free air

b Beta rays

1 5 roentgens equivalent (~140 erg/gm) per week measured at the basil layer of the epidermis which is taken to lie at a depth of 7 mg/cm² below the surface of the skin

c Neutrons

One tenth of the energy absorption permitted for gamma rays or in terms of incident neutron flux

2 20 Mev 30 neutrons/cm per second
0 5 2 Mev 50 neutrons/cm per second
Thermal neutrons 1200 neutrons/cm per second

2 *Partial body exposure* (8 hours/day 5 days/week)

X rays gamma rays beta rays If limited to hand and forearms 1 5 r (or its energy equivalent) per week at the basil layer of the epidermis

3 For operating purposes it is permissible that in any one week twice the weekly figures given above may be taken provided that the average over 3 months does not exceed the weekly limits

C *Military Emergency Doses*

75 roentgens in a single emergency operation or
25 roentgens in each of 8 emergency operations carried out at weekly or longer intervals

MAXIMUM PERMISSIBLE LEVELS FOR OCCUPATIONAL EXPOSURE TO RADIOISOTOPES

	MPL in body (millicurie) (UC/cc)	*MPL in air (UC/cc)*	*MPL in liquid media (UC/cc)*
$Ra^{2\ 6}$	0 1	8×10^{12}	4×10^{8}
$Pu^{\ 39}$	0 04	$\times 10^{1}$	$1\ 5 \times 10^{6}$
Sr^{89}	2.0	———	———
$Sr^{90}(+Y^{90})$	1.0	8×10^{10}	8×10^{7}
$Po^{\ 10}$	0 005	———	———
H^{3}	1×10^{4}	5×10	0.4
C^{14} (as CO in air)	———	1×10^{-6}	———
Na^{24}	15	———	8×10^{3}
P^{3}	10	———	$\times 10^{-4}$
Co^{60}	1	———	1×10^{-5}
I^{131}	0 3 (0 18 in thyroid)	3×10^{9}	3×10^{5}

Study of the peripheral blood count has been used since the establishment of body penetrating ionizing radiation as a cause of aplastic anemia in the hope that early effects would be so detected Depression in the white blood cell count can be demonstrated readily after exposure to sufficiently large doses with return to preexposure level three weeks

after removal from radiation (see Warren)[41] Kaufman[4] found a change in coagulation and prothrombin time in hospital workers exposed to minimal radiation for 7 years Nordenson[6] reported that 52 per cent of 1 166 individuals in radiologic work showed changes in the white blood cell series Dickie and Hempelmann reported in 1947 on the blood smear findings of 364 exposed and unexposed workers at the Los Alamos Scientific Laboratory They described intracellular bodies visible in the lymphocytes seen only in supravital preparations Dickie and Hempelmann found relatively more of these so called Dickie bodies in the lymphocytes of workers exposed to ionizing radiation than in individuals not so exposed They pointed out that this is not a specific effect as an increase in such intracellular bodies was observed in the lymphocytes of workers exposed to chemicals such as lead In general the interpretation of blood counts as an index of bone marrow effect following exposure to ionizing radiation of low level dosage is extremely unsatisfactory because of the many factors affecting blood count[43] Until a better tool is found they must be used In deciding whether or not an individual must be removed from work with ionizing radiation it is necessary to have complete knowledge of the nature of the worker's exposures past and present plus a sufficient number of previous blood counts In our present state of ignorance decision to remove workers from all ionizing radiation temporarily at least is the only reasonable protection available if changes in the total count of blood elements especially leucocytes or depression in the white blood cell elements especially lymphocytes persist

Knowlton[4] studied the complete blood counts of ten atomic energy laboratory workers who had weekly hemograms done over a 77 week period During this time the men received 0 2 roentgens of gamma radiation per week A small but significant fall in total white blood cell count absolute neutrophil and lymphocyte count was detected There was no evidence of ill effect on the health of the workers This study is important in considering possible long delayed result of repeated small doses of ionizing radiation throughout the working years of individuals It is likely the changes in blood count detected by Knowlton are benign and reversible and later studies by Carter[3] on this same group of individuals show return to normal values after a period of some six months without radiation exposure

Cyclotron workers have shown an unusual type of cell in the peripheral smear in a statistically significant number of cases The cell is designated as a binucleated lymphocyte It appears in the peripheral

blood smears of laboratory animals exposed to body penetrating radiation

It must be emphasized that the acute problem that faced industry and physicians just prior to and following World War 1 caused by ignorance of the devastating effects of radium and x rays is entirely different from the current problem The effect of low dosage radiation undoubtedly is different It is essential that a physician with a clinical problem in this field avail himself of adequate knowledge of the quality and quantity of his patient s exposure to ionizing radiation It has been known for some time that a distinctive type of cataract may develop in certain x-ray workers[19] We now know that Japanese survivors of the atomic explosion of 1945 show cataracts in a statistically significant number[1] Further certain research workers engaged in atomic energy development have shown a similar unusual cataract Cogan[9] reports that the cataractogenic dose of x rays of 100 kv energy or greater is cited as being between 500 and 1 000 r Fast neutrons and gamma rays are also held responsible for cataract formation so that modern practice calls for careful eye examination before beginning work around high energy equipment and care not to receive high doses to the eyes Ill effects now and in the future are more likely to be the result of foolhardy ill considered experiments by professional people too intensive x ray study of the population and the recognized hazard to radiologists and their helpers in routine work than from industrial exposure

DECONTAMINATION

In all work with radioactive materials natural and artificial elaborate protective equipment is mandatory as well as health monitoring already referred to[14, 10, 6, 76, 8] Coveralls caps gloves and canvas boots overshoes are regularly used to prevent contamination of body surfaces The interested reader is referred for details to the handbook Safe Handling of Radioisotopes prepared for the National Committee on Radiation Protection (by the Subcommittee on the Handling of Radioactive Isotopes and Fission Products)

In certain operations where inhalation of alpha emitters is a hazard respirators are used with knowledge of their shortcomings Engineering control must be relied on for protection of the workers The problem of cleaning protective clothing accidentally contaminated laboratory surfaces or vehicles of radioactive material has developed a new body

of procedure spoken of as a whole as decontamination This includes also the care of body surfaces or wounds so contaminated In general mechanical washing is the method of choice When washing does not remove surface contamination titanium dioxide paste kaolin or a saturated solution of potassium permanganate followed by a 5 % sodium bisulfite rinse have been discovered to be effective Instruments for detecting levels of contamination are made available in workrooms and first aid rooms to guide the decontamination steps necessary Occasionally if a wound becomes contaminated with radioactive material of such toxicity as plutonium excision of the tissue is done Langham has analyzed the results of 78 such procedures and could demonstrate the presence of plutonium in the excised tissue in only three instances Plutonium imbedded in tissue will be absorbed quickly and up to 80 per cent subsequently fixed in bone Workers at the Metallurgical Laboratory in Chicago have shown that as little as 1 microgram of plutonium placed beneath the skin of experimental animals will produce ulceration and other pathological changes These data indicate that each case must be treated according to the circumstances of the particular contaminated wound

The problem of disposal of contaminated waste from laboratories and water from decontamination procedures is taken seriously Some authorities drop cement sealed barrels of contaminated waste at sea believing that the factor of dilution makes this a safe method Others bury the material and surround such contaminated dumps with high protective fences and ample warning signs changing the dumping area from time to time In the case of radio isotopes of short half life the contaminated waste may be kept in a controlled area of the laboratory well labelled The advice of the National Committee on Radiation Protection is that the principal activity in a waste solution if possible should be precipitated and disposed of as active solid material Disposal of active solutions to public sewers and water systems is permissible if controlled It must be considered that the radioactive concentration may increase by 100 000 fold due to concentration in soil algae and similar organisms

Military Use of Atomic Energy

Military use of atomic energy described by Smythe in detail and its medical effects are here summarized Readers are urged to read some or all of the material in The Effects of Atomic Weapons prepared at

the request of the Department of Defense and the Atomic Energy Commission in 1950 which contains complete data on this subject[1]

What knowledge is available rests on the explosion of two atomic bombs in Japan at a height of 2,000 feet on a clear day[83]. These bombs were roughly equivalent to 20 000 tons of TNT. Buildings were damaged up to a limit of four miles from the place on the ground below the explosion, referred to as Ground Zero. Within a radius of more than one mile all buildings were destroyed or severely damaged. Many people were killed or injured within this same area. Because of intense heat, light and highly penetrating ionizing radiation released at the time of explosion the atomic bomb differs from the most powerful conventional TNT bomb. Further, highly radioactive material referred to as the fallout may remain after the explosion and emit harmful radiant energy. The ground may become radioactive by the action of neutrons released in the atom bomb explosion and depending on the character of terrain and objects with such induced radioactivity, ionizing radiation of varying potential danger may be produced. If the bomb burst is high in the air there is less likely to be dangerous radioactivity on the ground but great destructive force from such an explosion. However a bomb exploded on the ground or at low altitude will produce radioactive dust of pulverized materials and cause a limited area of great contamination. An underwater explosion of an atomic bomb as the Bikini test proved will produce great radioactive contamination of nearby land areas. The explosive effect producing burns and injuries would be greatly reduced by this type of explosion.

Depending on the differences related to the kind of atomic bomb explosion described above the radiation hazard is most serious within the first two minutes after explosion for those people within a mile of ground zero if they are without protection. This is most true in the case of air burst, less important in low level bursts and negligible in underwater bursts. Body penetrating gamma rays and neutrons cause the biological damage in this initial radiation insult of the bomb.

Following a low level underground or underwater atomic bomb explosion beta particles and gamma rays from fission products and alpha rays from unfissioned bomb material cause a radiation hazard. Also induced activity in terrain and nearby objects may cause added beta particle and gamma ray emission. The gamma rays cause a problem as an external hazard, the alpha and beta particles by becoming attached to dusts, food or the drinking water supply may by inhalation or ingestion become long term problems of internal radiation. If the half life of

these residual radioactive materials is of sufficient length they may produce malignant change or bone marrow depression by bombardment of tissue locally.[3, 85]

Direct injuries to lungs and gastrointestinal tract by the shock wave of the explosion were not common in Japan in 1945. However there was a high incidence of trauma from falling buildings, flying glass and other objects. Flash burns from the intense radiant heat of the explosion were many, as were flame burns from the many fires started. Bizarre protection from flash burns was dramatically offered by white materials which reflected the radiant heat.

From the Japanese experience it is estimated that fifteen to twenty per cent of the survivors of an atomic bomb explosion would suffer radiation sickness. Radiation sickness is caused by exposure of the whole body to a sufficiently high dose of body penetrating radiation to produce a distinctive set of signs and symptoms known as the acute radiation syndrome. This syndrome is to be sharply differentiated from radiation injury to local tissue such as the burns received by careless x-ray technicians. In the course of testing atomic weapons several workers received serious burns from high intensity beta radiation. This was described in detail by Knowlton and his associates.[4] Several much milder beta burns have been received by workers in atomic energy development research. These burns are troublesome not only because of immediate tissue damage but later possible malignant change in the injured skin. Hempelmann and his associates[34] have described in detail their careful studies of acute radiation injury following an accident in an atomic energy development laboratory. The acute radiation syndrome is well described in the following table.

There is no specific therapy for acute radiation sickness.[7, 8, 83] Because of depression of the hematopoietic system antibiotics are needed to combat infection. Blood transfusions are required after disturbance in the blood elements appears but no benefit has been demonstrated by supplying whole blood as a preventive. In an emergency whole blood will be needed for the victims of burns and trauma. Specific therapy for the tendency to bleed will be used as it becomes available.

Definitions

Because it is not likely that many physicians will be familiar with the units of measurements in current discussion of ionizing radiation, a few definitions are given on page 663(172).

SUMMARY OF CLINICAL SYMPTOMS OF RADIATION SICKNESS

Time after exposure	*Lethal dose (600r or more)*	*Median lethal dose (400r)*	*Moderate doses (300-100 r)*
First week	Nausea and vomiting after 1-2 hours Short or no latent period Diarrhea Vomiting	Nausea and vomiting after 1-2 hours No definite symptoms	No definite symptoms
Second week	Inflammation of mouth and throat Fever Rapid emaciation Death (Mortality probably 100 per cent)		
Third week		Beginning epilation Loss of appetite and general malaise Fever	Possible symptoms Epilation Loss of appetite & general malaise
Fourth week		Severe inflammation of mouth and throat Pallor Petechiae diarrhea and nosebleeds Rapid emaciation Death (Mortality probably 50 per cent)	Sore throat Pallor Petechiae Diarrhea Moderate emaciation (Recovery likely unless complicated by poor previous health or superimposed injuries or infections)

Reprinted from page 347 of *The Effects of Atomic Weapons*

Alpha — Greek letter used to designate rays consisting of helium nuclei Mass of alpha particles = $6\ 7 \times 10^{4}$ gm

Beta — Greek letter used to designate ray consisting of electrons from radioactive elements

Curie — Radioactivity equal to that produced by 1 gm of radon in equilibrium with the parent element radium $37\ 1 \times 10^{9}$ disintegrations/sec

esu — Electrostatic unit of electrical charge the amount of electric charge which in a vacuum will repel a like charge at a distance of 1 cm with a force of 1 dyne

ev (Electron Volt) — The amount of kinetic energy that is imparted to an electron by 1 volt $1\ 6 \times 10^{1}$ ergs

Gamma — Greek letter designating electromagnetic radiation or photons of nuclear origin similar in type to x ray

kev — Thousand electron volts

kv — Thousand volts

mev — Million electron volts

n — Neutron Uncharged penetrating highly damaging particles Depending on their speed they can penetrate several feet of tissue

Roentgen or r — Unit of x or gamma rays the amount which will produce 1 esu of charge in c c air under standard conditions

REM — Roentgen equivalent man or the amount of radiation equal in biologic effect to 1 r of x or gamma rays

REP — Roentgen equivalent physical or amount of radiation equivalent in energy production to 1 r of x or gamma rays or $1\ 6 \times 10^{1}$ ion pairs per gm /air

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By Alice Hamilton and Rutherford T Johnstone

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Coal Tar Benzene or Benzol

Coal tar benzene or benzol is the most dangerous of the industrial solvents with the exception of tetrachlorethane It is so recognized in industry and its use has been abandoned often at a good deal of sacri

fice by conscientious employers who refuse to subject their workers to such a risk

Benzene was brought to the attention of the medical world first in 1897 when Santesson[16] a Swedish toxicologist read a paper before the International Medical Congress in Moscow in which he described 9 cases of hemorrhage under the skin and from mucous membranes in girls using benzene rubber cement in a tire factory 4 of these cases ending in death Then 13 years later Selling of Johns Hopkins reported 3 similar cases in girls using a benzol rubber seal for tin cans Selling made many experiments on animals and established the basic facts underlying the pathology of benzene poisoning namely that it acts chiefly on the blood forming tissues the marrow of the bones and the lymphatic structures producing anemia and granulocytopenia together with a loss of the clot forming substances in the blood

The clinical picture that emerges from these early studies is one of progressive weakness dizziness headache and vomiting then the appearance of purpuric spots on the skin bleeding from gums throat nose and uterus and in fatal cases death from severe hemorrhage or toxemia

Selling's work in the experimental field was confirmed by many students who found that in animals the most important effect is leucopenia the fall in the red cell count is far less striking, the most important change found postmortem is aplasia of the bone marrow damage to the lymphadenoid tissues is far less important Among the leucocytes the polynuclears suffer the most In the early stage of poisoning stimulation of cell production is seen in the marrow accompanying the destructive process Regeneration can occur after an advanced degree of aplasia Benzene also is a direct leucotoxic poison acting on the white cells of the circulating blood

Other features were added to Selling's findings Duke[9] found in rabbits a rapid rise in the platelet count followed by a rapid fall while the bone marrow showed almost complete absence of megacaryocytes Animal experiments also showed the effect of benzene on the formation of antigen Rusk[4] found a reduction in the formation of lysin for sheep's blood and of precipitin Simonds and Jones[5] a loss of hemolytic and agglutinating substances Hektoen , a loss of lysin and precipitin Winternitz and Hirschfelder[63] reduced resistance to pneumococci White and Gammon[9] to tubercle bacilli Camp and Baumgartner[4] found that benzolized animals failed to have a normal reaction to injuries produced by heat chemical irritants and unsterilized foreign

bodies i e no leucocytosis and no increase of leucocytes in the injured area

Those years produced more careful experimental work with benzene than clinical studies and because of this a standard for diagnosis emerged which was based on animal response not on human

It is a serious error to assume that all the observations made on animals are true of human beings with benzene poisoning for there are marked differences Thus Hurwitz and Drinker found only slight signs of hemorrhage in their experimental rabbits and as a rule no prolonged bleeding time Even more important is the difference in the degree of anemia In animals leucopenia is far more striking than anemia and it was assumed for many years that that was true also of benzene poisoning in working people therefore that the earliest and most trustworthy sign was a fall in the white cell count below 5 000 a red cell count being unnecessary Many early cases must have been missed under this mistaken procedure for in man the loss of red cells may be greater than the loss of white cells and it may appear earlier

Acute benzene poisoning is of little importance under modern industrial management The danger is well understood and no longer are men sent unprotected into tank cars or vats It is a narcotic poison which acts with great swiftness producing unconsciousness or helpless confusion In such cases it is often the rescuer exerting himself to save the victim who gets a fatal dose while the passive victim survives As a usual thing recovery in non fatal cases is complete with no sequelae

Chronic poisoning is far more important It comes on slowly the symptoms are vague and often it is not till the stage of hemorrhage has been reached that the victim seeks help The bleeding may be from the nose the gums the uterus into the subcutaneous tissue more rarely into the retina or stomach or intestines An examination of the blood at this stage shows marked changes an anemia of the non regenerative type a granulocytopenia prolonged bleeding time and delayed clotting In such cases the diagnosis is easy if benzene exposure has taken place The process may be halted under appropriate treatment or it may progress even to a fatal ending without any further exposure This fact is stressed by Selling and Osgood and a number of such instances are to be found in the literature (Rohner Baldridge and Hausman[11] Anderson[1])

For the physician the most important task is to detect benzene poisoning in the early stage before serious damage has been done Blood and urine examinations should serve to reveal this stage

Theoretically there should be a stage of marrow stimulation with high blood cell counts and immature forms and actually this stage has been observed Teleky and Weiner found in the blood of women benzene workers nucleated red cells anisocytosis and poikilocytosis Ross Smith[53] found a high red cell count over 5 million in 14 out of 71 women also an increase in large epthelioid cells

As for the diagnosis of benzene poisoning in the very early stage opinion has changed very decidedly in recent years As the study of benzene poisoning in man has proceeded the single picture formerly established has had to be abandoned and the fact accepted that benzene is a bone marrow poison whose action may be exerted now on one element of the marrow now on another There may be polycythemia or anemia leucocytosis (polynuclear or lymphatic) or leucopenia there may be a complete absence of youthful forms or abnormal forms there may be reticulocytes myelocytes anisocytosis and poikilocytosis eosinophilia megalocytosis The color index may be low, normal or high Benzene is a bone marrow poison but the attack may be now on one element now on another, indeed there is evidence to show that a stimulation of one may go on at the same time as destruction of other elements[19, 48]

Donald Hunter[6] saw an illustrative case in a young girl who was exposed for 4 years to fumes from a mixture of 7 per cent benzene with Russian benzine which contains a fairly high percentage of ben zene On her first examination she was clinically well except for purpura of the limbs and a past history of menorrhagia The first blood count showed a reduction only of platelets 51 000 and of polynuclear leuco cytes 40 per cent but the red count was 5 100 000 the white 7 600 However only 48 hours later she had severe bleeding from the gums lungs and gastrointestinal tract The platelets disappeared from the circulating blood the red cells fell to 1 000 000 but the white cells rose to 15 000 Under a mistal en diagnosis splenectomy was performed and the peritoneal cavity was found full of blood She survived the operation and slowly recovered the platelets reappeared 13 000 in the second weel the red cell count rose to 3 300 000 white cells were 8 700 with polynuclears 31 [illegible] per cent Another English report by Hamilton Paterson[9] in 1941 confirms these findings The author de scribes 3 cases of poisoning one fatal and also the blood changes in 18 other women exposed to benzene The blood picture varied greatly anemia polycythemia leucopenia leucocytosis relative decrease rela tive increase of polymorphonuclears and eosinophiles

Andersen's[1] case is a contribution to the literature of atypical benzene poisoning Here there were several interesting features The disease developed about 5 months after exposure and continued to progress for 18 months after exposure had ceased death was caused by general septicemia streptococcus hemolyticus the red blood cells showed marked variations in size and shape with polychromatophilia and basophilic stippling Two normoblasts were seen The polymorphonuclear cells were young showing a marked shift to the left A few weeks before death the reticulocytes made up to 1 3 per cent normoblasts 10 per cent and there were monocytes myelocytes and myeloblasts Autopsy revealed hyperplasia of the marrow and acute splenic tumor

A recently discovered aid in the diagnosis of early benzene poisoning is the urinary test devised by Schrenk Yant and Sayers[1] of the Bureau of Mines They found uniformly in a series of about 100 animals an early sign of benzene poisoning in the urine namely a decrease in the proportion of inorganic sulphates to total sulphates this decrease being marked in accordance with the severity of the intoxication The same decrease was found in benzene workers

Normally the inorganic sulphates make up 85 to 95 per cent the organic ethereal or conjugated 5 to 15 per cent but in cases of benzene absorption the phenolic products that are formed take up the sulphur and the result is an increase in the conjugated sulphates which reverses the above proportions The most important fact relating to this test is that the decrease occurs rapidly on exposure to benzol and well in advance of leucopenia or anemia or other evidence of damage [1]

In other hands this test has proved of minor value The studies made by the Boston and New York groups[2] showed that it failed in some cases of clinical poisoning and could not be depended on to reveal absorption of benzene Like conclusions were made by the Public Health Service

Vigliani[1] who has seen many cases of benzene poisoning in Italian rubber works divides them into four classes (1) those clinically hematologically and anatomopathologically typical of aplastic anemia ( ) those clinically typical of aplastic anemia but showing an active hemopoiesis especially in the bone marrow pseudo-aplastic anemia (3) those with atypical aplastic anemia with myelitic hyperplasia or metaplasia resembling leucemia especially in liver and spleen (4) those with chronic or acute leucemia not infrequently appearing as aleucemia All those forms have been demonstrated experimentally in animals

As to the fourth class evidence is piling up that leucemia myeloid or lymphatic may be one of the forms benzene poisoning may take Penati and Vigliani[1] collected 10 cases, which had been reported by 1938 and Mallory and his colleagues have added two

It may be well to give a brief summary of the newer additions to our knowledge of this form of industrial poisoning which we owe to the studies made by a group in New York (Division of Industrial Hygiene State Department of Labor and Hospital of the Rockefeller Institute) and a group in Boston (Division of Occupational Hygiene State Department of Labor and Massachusetts General Hospital)

(1) The diagnosis of benzene poisoning mild or severe must be made on the whole blood picture and the earliest and most frequent deviation from the normal consists in a fall in the red cell count and an increase in the mean corpuscular volume of the red cells A fall in platelet count and a reduction of hemoglobin follow in frequency but a fall in the white cell count is less characteristic of early poisoning than any of the above Anemia and macrocytosis are the changes to be looked for

(2) Increase of urobilinogen and deviation from the normal urine sulfite proportions were not found to be of value in diagnosis

(3) Bleeding time and coagulation time were of no aid being prolonged only in severe cases

(4) *Clinical symptoms weakness fatigue epistaxis dryness of the throat anorexia nausea dizziness insomnia* were of dubious value because although they were present in workers exposed to benzene more than in controls they were absent in some case of serious poisoning

(5) Purpura particularly bleeding from the mucous membranes was relatively rare being absent in some severe cases

(6) In severe poisoning the blood may show changes like those in pernicious anemia Erf and Rhoades noted a feature of benzene intoxication which may prove helpful in distinguishing it from per nicious anemia namely that free hydrochloric acid is present in the gastric juice

(7) An aplastic marrow is not typical of benzene poisoning hyperplasia may be found even more often In 16 cases 12 men and 4 women the 4 women all showed aplasia but only 2 of the 12 men the other 10 showed hyperplasia This seems to point to a tendency of the male to react with hyperplasia of the female with aplasia and sug gests that the belief that women are more susceptible to benzene than

men may be based on the failure hitherto to recognize the hyperplastic form of the disease

(8) A study of the hyperplastic cases reveals what may be called a neoplastic tendency rapid growth as shown by mitotic figures the development of cells having no counterpart in normal tissues but common to a variety of malignant tumors In a case seen by one of us (R T J) the marrow was full of mitotic figures and there were occasional giant cells with monstrous nuclei suggesting a neoplastic tendency A close similarity between these hyperplastic marrows and those described by Martland[11] in chronic radium poisoning was noted and in both cases there is a prolonged latency and a tendency to progress for months or years after exposure has ceased

The influence of benzene on the course of infections in animals has been reviewed Clinical cases confirm these facts Thus Rohner and his colleagues[11] noted as an outstanding feature the decided lack of response on the part of their patient to infection Of Hunter s[1] first 4 cases those that died had septic temperatures as did Selling s first case but the that recovered did not Meda[11] reported a case of prolonged suppurative cysto pyelonephritis Smith[3] reported one of obstinate suppuration of the axillary lymph nodes another of abscess in the thigh Severe lesions of the mouth are the most frequent manifestation of this action of benzene and Vincent s angina was noted in several cases Martland (see reference no 19) saw osteomyelitis of the lower jaw and gangrenous stomatitis Loewy s[9] case was one of death from gangrenous osteomyelitis of the jaw and gangrene of the lungs

It is probably true of working people poisoned by benzene as it was of the early cases of radium poisoning that a diagnosis of Vincent s angina or osteomyelitis was made in many cases without inquiry into a possible occupational cause

The use of benzene has increased not only because of the demand for toluene for explosive production but because the new method of distilling petroleum at a great heat cracking * results in a gasoline or naphtha containing coal tar bodies benzene among them sometimes in a high proportion The manufacturer may believe he is using a safe solvent free from benzene when actually there is a dangerous amount of benzene present

Cracking petroleum means heating it above its decomposition point in order to crack" or break up the large molecules of the heavy hydrocarbons to form smaller molecules of the lighter Aromatic compounds begin to appear at 800 F and at 1,000 F the amount is appreciable

The American Standards Association has pronounced 100 parts per million to be the maximum allowable concentration of benzene

Toluene (Toluol) Methyl Benzene and Xylene (Xylol) Dimethyl Benzene

The textbooks say that toluene is a stronger narcotic than benzene but that is based on animal experiments with measured quantities of vapor In practical life the greater volatility of benzene makes the danger of narcosis much greater than with toluene or the still heavier xylene In fact it is very rare to hear of a case of acute toluene poisoning of any severity still rarer of xylene poisoning

As for chronic poisoning Batchelor (see ref 62) of the Public Health Service tested toluene xylene and that mixture of *higher homologues* called solvent naphtha or hi flash naphtha and failed to produce in any of the animals the severe anemia and leucopenia of benzene poisoning nor did Winternitz[63] find a loss of defensive bodies in the blood In Selling s[9] experiments with toluene there was destruction of leucocytes but far less than with benzene and it was compensated rapidly Hektoen[3] found no marked changes in the bone marrow or in the absolute or relative white count

According to Cushny toluene is oxidized in the body to benzoic acid and then combined with the glycocol of the body it is excreted as hippuric acid Benzene is oxidized to phenol and dioxybenzol which combine in the kidney with sulphuric and glycuronic acids to form conjugate acids and the corresponding dioxy compounds

Nevertheless from all the industrial countries Germany especially come contradictory reports concerning the two methyl derivatives of benzene some asserting the safe character of these solvents others the contrary Reports have appeared from England and from Germany with claims that toluene and xylene have been proved to exert an *action on the blood forming tissues which differs not at all from that of* benzene Most of the German cases were in printing establishments probably in rotogravure work where large quantities of xylene or xylene and toluene seem to be used[38, 56] For instance there is the case of a lithographer who was exposed for a long period to xylene fumes and died of aplastic anemia The autopsy showed severe damage to the bone marrow atrophy of lymphoid tissue and complete atrophy of the normal cellular elements in spleen and lymph nodes There were

also 1 cases of poisoning in German color printers who showed leucopenia and thrombopenia but in only [illegible] cases a reduction in red cells Here however benzene was used in addition to the other two Gerbis who has had a long experience in the German factory inspection service says that the cases in the printing industry are severe in proportion to the amount of benzene present in the solvent and that toluene and xylene are far less harmful One of the recent series of experiments on blood changes from these two homologues was reported by Engelhardt[illegible] who found a decrease in the number of red cells after exposure to high concentrations a proportionately lowered hemoglobin a marked leucocytosis and a considerable fluctuation in the proportion of lymphocytes to polynuclears These are of course far less severe changes than those caused by benzene So far Ferguson and his colleagues[1] are the only ones who insist that toluene and benzene have an identical effect on the blood They tested the two on rabbits and rats and found that while benzene is the more toxic probably because of its greater volatility the effects of the two on the blood forming organs are similar first stimulating the formation of young blood cells then producing leucopenia anemia and thrombopenia They also describe a case of agranulocytic anemia in a workman exposed to toluene (see also R H Wilson[illegible]) Smyth and Smyth[34] observed in experimental toluene poisoning signs of early toxic damage in the cells of liver and kidney and some pulmonary inflammation but only after inhalation of heavy fumes

The authors of this chapter have had confidential communications from several industrial physicians who have had disappointing results following a change from benzene to toluene Instead of a disappearance of the leucopenia and anemia there was little if any change in the blood in one instance even after the lapse of 3 years In fact not only did the low counts persist but some women whose blood counts had been normal at the time benzene was discontinued developed polynuclear leucopenia and low red cell count and low hemoglobin while working with toluene This is a puzzling situation One does not know whether to assume a persisting action of benzene even after exposure has ceased or a combined action the toluene continuing the damage begun by the benzene A striking instance of this is a case of fatal aplastic anemia reported to one of us (A H)

A leather worker was exposed to benzene continuously from 1918 to 1928 and thereafter was exposed to a substantial quantity of toluene vapors from 1928 to 1931 when he was disabled and six months later died of aplastic anemia with typical blood changes The autopsy was

performed by Martland who found an aplastic marrow and the award was rendered in favor of the widow and dependents on the ground that exposure to toluene can produce chronic poisoning or aggravate a benzene poisoning previously acquired

A number of mass observations of workers exposed to toluene have been made in recent years Greenburg and his colleagues[17] examined 106 painters and a control group of 430 fur workers The concentration of toluene in the workrooms ran from 100 to 1 100 parts per million Sixty one painters had had no exposure to other solvents 45 had had exposure to other solvents 30 of them to benzene The comparison with the controls ran as follows, enlarged liver painters 30 per cent controls 7 per cent, in the 61 with no previous exposure only [illegible]1 4 per cent had enlarged liver but even this is three times the control rate There was in the painters group a slight decrease in the red cell count and a slight lymphocytosis the mean corpuscular volume was somewhat increased in 23 6 per cent (controls 7 [illegible] per cent), the hemoglobin was higher values of 16 gm per 100 or more were found in 37 7 per cent as contrasted to [illegible] 4 per cent of the controls All these deviations from the normal were slightly more marked in men who had had previous exposure to benzene

The Public Health Service[11] tested concentrations of toluene from 50 to 800 ppm (parts per million) on three normal subjects and concluded that inhalation of 200 ppm for 8 hours causes slight but definite impairment of coordination and reaction time which is liable to increase the danger of accidents, with higher concentrations these effects increased and at 600 to 800 ppm they could be observed after a few hours exposure The elimination of hippuric acid in the urine increases with the concentration of toluene in the air but the ratio of inorganic to organic sulphates is not affected by toluene nor was there any sign of injury to the blood forming organs

The latest study of toluene exposure in a large group is that of Rex H Wilson[61] who was able to follow the history of some thousand employees working with commercial toluene for one to three weeks in concentrations from 50 to 1 500 ppm One hundred showed symptoms severe enough to send them to the hospital for examination and 10 of these showed blood changes There were no deaths Those exposed to concentrations no higher than 200 ppm were practically unaffected at [illegible]00 to 500 ppm headache was complained of and there developed nausea anorexia bad taste in the mouth lassitude slight but definite impairment of coordination and reaction time, but no significant phys

ical or laboratory findings were noted When the concentration of toluene was over 500 ppm all the above disorders were increased some times markedly and in several cases petechial hemorrhages appeared under the skin

In most of the cases the blood picture was normal except for a fall in the red cell count usually down to 2 500 000 Leucopenia was found in only 2 cases with white cell counts 500 to 3 000 here all the other blood elements were reduced and biopsy of the bone marrow disclosed partial destruction of the blood forming elements

In dealing with commercial toluene and xylene it must never be forgotten that both are very likely to contain benzene The ordinary method of distilling these bodies does not make for their complete separation nor is it necessary in industrial use to have pure products

The maximum allowable concentration for toluene has been set by the American Standards Association at 00 ppm (parts per million) for xylene at 200 ppm

Benzene Derivatives

The derivatives of the benzene ring are numerous they are indus trially important and they are of course extremely complex New ones are introduced continually too rapidly to allow the toxicologist to keep pace with the chemists who produce them and as a result we have here a most obscure and difficult field for the industrial physician Sometimes it is possible to predict from the chemical composition of the simpler members of the coal tar group what the physiological action probably will be although even here the problem of the isomers enters for of three compounds with the same formula the one in the para position may differ in its action from the one in the ortho position and both from the one in the meta position Thus the toluidins are toxic in this order para first then ortho then meta The French high explosive melinite is a mixture of trinitrophenol and of the isomer of dinitro phenol which has the two NO groups and the HO group attached to the ring in the 1-2 4 position The isomer proved during World War I to be highly toxic with a characteristic action which was not shared by any of the others Later on its use as an anti obesity drug amply confirmed the French observations There is also a decided difference in the toxicity of substitution products formed by displacement of the hydrogen in the ring and those formed by displacement of hydrogen

in a side chain An example of the former is toluidin which is very toxic of the latter benzylamine, which has the same written formula but is fairly harmless Many other illustrations could be given but these are sufficient to indicate some of the complexities of the subject

According to Fraenkel[11] the entrance of the HO nucleus to form the phenols naphthols and cresols increases toxicity but industrially these bodies give very little trouble except in the matter of burns with a very rare case of extensive skin absorption followed by collapse and death The entrance of chlorine into an aliphatic compound increases its toxicity but the reverse is true of an aromatic compound The chlorbenzenes are less toxic than benzene The nitroso group and the nitro group always increase toxicity but when a nitro compound is reduced to an amino as when nitrobenzene is reduced to aniline the toxic characteristics remain much the same but the intensity of action is lessened

ANILINE NITROBENZENES NITROTOLUENES

According to some authorities all of the clinical manifestations of poisoning by the nitro and amino benzene derivatives may be explained by the formation of methemoglobin and the resulting oxygen starvation but in very rapid and severe poisoning a direct action on the central nervous system takes place before methemoglobin is formed (Heubner[4]) Clark Van Loon and Morrisey[5] testing animals with aniline decided that the most important action is the formation of methemoglobin with resulting anoxemia and depressant action on the central nervous system which is specially sensitive to anoxemia With this Young and his colleagues[6] agree but add a direct toxic action as shown by a marked fall in blood pressure and cardiac arrhythmia

The effect on the bone marrow is at first to stimulate active red cell production as shown by polycythemia although sometimes with low color index and then inactivity follows There are evidences of effort at regeneration stippled red cells polychromatophilia nucleated forms variation in size and diminished platelets An early leucocytosis is followed by a lymphocytosis The blood often is chocolate colored and appears thicker than normal It may be impossible to make hemoglobin estimations by means of color scales for the methemoglobin changes the color of the blood

The smoky or dark brown or port wine color of the urine is noticed

by the men themselves as an early sign of poisoning. Hemoglobin has been demonstrated in the urine, also hydrobilirubin and hematoporphyrin. A reduction compound is found in the urine in some cases and serves as a proof that absorption is taking place. These are para-amino-phenol from aniline; the nitrobenzenes and nitroanilines; amino-nitro-4-phenol from dinitrophenol; dinitro-hydroxylamino-toluene (Webster test[3]) and 6-dinitro-4-aminotoluene (Snyder and von Oettingen test[59]) from trinitrotoluene.

Certain of the nitro and amino compounds are conspicuous as causes for occupational poisoning. Thus the British factory inspectors list cases almost every year from exposure to the intermediates DNB, DNT and TNT; from the making and use of aniline; from aniline black dyeing and from dinitrochlorbenzene. "Anilinism" is the term under which these cases are listed and under this term reports have been made since 1930. Some of the histories show clearly that skin absorption plays an important part in such poisoning. For instance, a workman carrying a bucket of aniline slipped and splashed it over his coat and arms. He took off his coat and washed his arms, but then put on his coat again. Some hours later he became cyanosed, was dizzy and drowsy, and when removed to the hospital was only semiconscious.

A case which illustrates this point was seen by one of us (R. T. J.). This was in a chemist's assistant who spilled nitrobenzene on his trousers and almost at once fell to the floor. He was rushed to the hospital in his soaking clothes and was unconscious when he arrived, with respiration at first rapid, then slow and irregular, pulse feeble, heart sounds distant and weak, cyanosis marked. A sample of blood was of a deep brown color. He died an hour and a half after the accident. Postmortem examination revealed nothing of note.

Volatile liquids such as aniline act more rapidly than solids, as, for instance, trinitrotoluene. When poisoning is slower there is a toxic action on bone marrow and liver and acute degenerative hepatitis may result with or without aplastic anemia. TNT is the substance which has given rise to the great majority of such cases in the literature, but an unusually slow form of dinitrobenzene poisoning has been known to result in the same liver lesions.

Prosser White[60] has described dinitrobenzene poisoning as he saw it in British explosives manufacture in World War I. The poison passes rapidly through the skin and also is inhaled as vapor. A workman who breathed for ten minutes the air in a flue through which pure dinitrobenzene had been poured from the mixing pans died eighteen hours

later from the effects Such cases were rare, but chronic poisoning was far from rare This was characterized by a severe form of anemia the skin was dusky yellow, the conjunctivae jaundiced the man looked as if he were suffering from partial asphyxia his muscles were wasted sensation dulled paresis of the hands was marked there were paresthesias hyperesthesia and defects of vision

Almost all of the compounds of this series seem capable of setting up a more or less severe dermatitis, although some are far worse than others According to White[60] the intermediates which are responsible for lesions of the skin are the following in the order of their injurious action dinitrochlorbenzene dinitrophenol, p nitrosophenol p nitrosocresol diaminophenol p nitroaniline p-aminophenol

Dinitrophenol

Dinitrophenol 1 2-4 or alpha dinitrophenol was a constituent of the French explosive melinite and is also an intermediate in dye production, for a while it came into use in the treatment of obesity It is a powerful stimulant to metabolism According to the French investigators Etienne Martin and A Meyer (see Perkins[42]) the mechanism of intoxication consists in an enormous increase in the intracellular oxidation processes with consequent increase of gaseous exchange from ten to twelve times the normal and rise of body temperature *in spite* of the distension of skin capillaries and profuse sweating This excessive oxidation affects metabolism and nutrition and damages liver and kidney cells Unchanged dinitrophenol and the reduction products amino and diamino nitrophenol are found in the urine There are absolutely no pathological findings at autopsy

The use of alpha dinitrophenol for the treatment of obesity has led to a number of cases of serious poisoning with symptoms such as those described above and in 4 cases with agranulocytosis (see Silver[51]) It should not be used for this purpose The pronounced toxicity of this compound should lead to great caution in its industrial use, which unfortunately is increasing

Dinitrocresol

Another compound of increasing importance in industry is 3 5 dinitrocresol which has an action similar to that of dintrophenol, being

in the opinion of some observers less toxic, of others more toxic. It has been used also in the treatment of obesity and has been responsible for severe and even fatal poisoning (von Oettingen[40]). Industrial poisoning has been described by a German (Schwarz[illegible]) and recently by J. M. McDonald[illegible] of the Bureau of Occupational Diseases of the Baltimore City Health Department. McDonald's case was in a negro whose palms and soles were dyed a deep canary yellow and who recently had lost [illegible]0 pounds. He had a temperature of 102° F., a phenomenal basal metabolism rate of 400 plus, rapid pulse, rapid respiration, profuse sweating, shortness of breath and cough. An examination of his work place showed he had been exposed to 4.7 mgm. of dinitrocresol dust per cubic meter of workroom air per day. The man recovered.

Paraphenylenediamine

Paraphenylenediamine is used very generally as a dye for furs, known in industry as ursol. It is a notorious cause of dermatitis both in fur dyers and fur wearers and also it has been known to set up in susceptible individuals typical attacks of bronchial asthma, which are attributed by Hanzlik[1] to direct irritation of the air passages, by Mayer[2] and others[3] to an allergic reaction.

Nitroanilins, para and *meta*, are important intermediates in dye manufacture and cases of severe poisoning have been reported following overexposure to fumes or dust. The symptoms are characteristic of the aniline group as already described.

Chlorotoluidine

An amino compound, 5-chloro-o-toluidine, has caused a good deal of trouble recently in some English factories, the intoxication being characterized by cyanosis, tachycardia and hematuria with subsequent albuminuria, strangury and frequent micturition. The bladder is affected chiefly, the kidneys more slightly. For further discussion of this and for the 4-chloro and 6-chloro isomers see von Oettingen.[40]

Betanaphthylamine

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the Webster test[16] to give warning of approaching danger. This color test revealed the reduction product. It is, however, proof only of absorption. Kennedy and Ingham[8] prefer a simple test for the determination of porphyrinuria, which shows intoxication. Snyder and von Oettingen[51] propose a new test more sensitive than the Webster test for a reduction product in the urine which they tentatively identify as [illegible]-6-dinitro-4-aminotoluene.

Experience in England indicates that women are more susceptible than men to TNT; colored men less than white. The greater susceptibility of youthful workers was demonstrated in American plants during World War I.[19]

Tetryl

Tetryl is trinitrophenylmethylnitramine, a very important military propellant. Tetryl dermatosis was recognized during World War I as a very troublesome affection, but it was believed that this was the only form of poisoning to be looked for in tetryl workers. More careful studies made during 1943 reveal the fact that systemic effects also may occur. Witkowski and his colleagues[61] report no less than 1,[illegible]58 cases of industrial illness due to tetryl in a force of over 5,000 workers. The chief complaint was of a dermatitis, usually on the face and neck. Epistaxis was a common complaint and small ulcerations of the nasal mucosa furnished the cause. A systemic effect was seen also. Anorexia, mild nausea, flatulence and abdominal cramps occurred in 10 per cent of all exposed; dry cough and pain in the chest, headache, irritability, sleeplessness, lassitude were frequent complaints. Three cases were serious enough for hospitalization. All had a history of severe tetryl dermatitis which recurred with increased intensity on a second accidental exposure. The authors emphasize also the occurrence of rapidly developing secondary anemia. Noro[[illegible]] of Finland observed anemia in 109 of 163 tetryl workers.

Chlor Compounds of Benzene: Nitrochlor

Chlor compounds of benzene are used largely in industry, notably paradichlorbenzene, which is a constituent of drugs, anti-moth mixtures, insecticides, etc. It gives rise to dermatitis, but if systemic symp-

of them *betanaphthylamine*, plays in the production of bladder tumors. For further discussion of this see Section XXXIII of this chapter which follows this section. In the experience of one of us (A.H.) both are capable of producing symptoms of "anilinism" but in practice the alpha isomer gives little trouble while the beta may cause cyanosis and frequent micturition from the presence of the carcinogenic substance.

Trinitrotoluene: TNT

This was studied exhaustively during World War I especially by the British and experience during World War II has not added much to the facts accumulated in 1914-18. It is highly toxic both locally and after absorption. It produces a sago grain dermatitis intensely irritating with exfoliation appearing on hands and forearms chiefly but wherever the skin is exposed or touched with TNT smeared fingers. In American plants there was invariably an increase of dermatitis in hot weather not only because arms and necks were more exposed but because the sweat helped to dissolve the TNT dust and quicken its absorption. Because TNT is absorbed through the skin the mixture of nitrate of ammonia and TNT known as amatol, is more productive of poisoning than pure TNT. Ammonium nitrate is hygroscopic and keeps the skin of hands and forearms moist thus dissolving the TNT.

TNT belongs to the group of poisons which enter through the skin and which form methemoglobin.[8] Cyanosis is a characteristic symptom. The usual case of "TNT sickness" shows pallor, bluish lips and lobes of the ears, breathlessness, feeling of tightness in chest, abdominal pain, nausea, headache, lassitude, anorexia. Jaundice is a serious sign of liver damage and no worker who has recovered from such an attack should ever be exposed again (Hilton and Swanton[5]). TNT affects the liver, the bone marrow and the vascular endothelium in varying degree.[30] Severe intoxication therefore results in acute toxic hepatitis, toxic purpura and more rarely aplastic anemia. Evans[11] reports 7 cases of TNT jaundice with 3 deaths. Autopsy revealed acute yellow atrophy of the liver and hyperplastic bone marrow.

Coyer[6] reports 7 cases of TNT poisoning of the gastrointestinal type, one of them fatal. In this case autopsy revealed severe jaundice, cirrhosis of the liver with superimposed hepatitis and hemorrhage into the gastrointestinal tract.

In World War I physicians in charge of TNT plants depended on

a benzene hazard may arise and frequent physical as well as laboratory examinations are indicated

Men should be rotated and when the least variation from the normal is noted the worker should be removed from his exposure Likewise workers should be instructed to report for examination upon noting bleeding from the nose or gums or other mucous membranes or when unaccountable subcutaneous hemorrhages or discolorations are noted Safety engineers have done an excellent job of preventing accidents by educating the employees regarding the dangers which exist in certain types of employment It is high time for a similar educational campaign to be conducted in the various occupational diseases Many serious cases of poisoning from benzene and other noxious agents could be prevented if the employees themselves knew or were informed of certain early signs or symptoms To find a case of far advanced anemia in one who for some time had noted bleeding and other symptoms of general malaise without reporting these denotes not only ignorance on his or her part but a failure in education or instruction

Proper Ventilation —Obviously proper ventilation is extremely important Since benzene fumes tend to form pockets and are very diffusible and heavier than air the ventilation should be general and from the floor by means of suction

Dermatitis —Dermatitis is prevented by the rubbing of olive oil or other animal or vegetable fat into the skin or by the use of a wax ointment before handling the substance Rubber gloves may be used but ordinarily they do not withstand the action of benzene so synthetic rubber which resists the solvent action much better should be substituted

Anemia Blood Transfusions —In those workers who have developed anemias of varying degrees together with other symptoms of benzene poisoning the most valuable form of therapy is blood transfusion repeated frequently if necessary In attempting to carry out this type of therapy Gray Greenfield and Lederer[11] were confronted with a case of autohemagglutination although the patient had had three previous transfusions They point out that autohemagglutination is the interaction of the agglutinin of the serum with the agglutinogen of the red blood cell and can occur only at a temperature below that of the body They eliminated the difficulty by heating the serum and cells to body temperature

Liver Extract and Iron —Since the anemia frequently is of the microcytic hyperchromic type liver extract intramuscularly in large

toms arise in a sprayer of this compound, it would be well to learn what is the liquid vehicle for it might be benzene carbon tetrachloride or carbon disulphide

Nitrochlor compounds are more irritating to the skin than those without the nitro group and they produce systemic poisoning with methemoglobinemia of like character but less severe than that of nitro benzene (von Oettingen[40])

Diphenyls

Diphenyl an important intermediate for the newer plastics is two benzene rings linked together and is made by bubbling benzene through molten lead At ordinary temperature it is solid which may explain why no trouble has been reported from its use This is not true of its important chlorine derivatives

Chlorinated diphenyls are used for the same purposes and often in conjunction with chlorinated naphthalenes In their study of the latter Drinker and his colleagues[8] tested also chlorinated diphenyls and chlorinated diphenyl oxides They found that the former bodies act much as do the naphthalenes of low chlorine content and that the same limit of concentration in the air may be permitted 100 mgm per 10 cubic meters of air For the chlorinated diphenyl oxides the limit should be the same as that for the higher chlorinated napthalenes 50 mgm per 10 cubic meters Greenburg[16] has outlined the proper methods of protection against injury from these compounds

TREATMENT

Benzene (Benzol) and Its Homologues

What is said here of treatment for benzene may be applied to toluene xylene and a few of the less toxic homologues of benzene

Prophylaxis Frequent Physical and Laboratory Examinations — Constant vigilance by blood examinations and air analysis should be the established order wherever benzene constitutes a hazard The routine white cell count commonly resorted to should be supplanted by a complete blood study for reasons emphasized in earlier paragraphs of this chapter Only those in fine physical conditions should be placed where

a benzene hazard may arise and frequent physical as well as laboratory examinations are indicated

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dosages 15 to 30 units daily for four days then every two or three days, or ventriculin orally 15 to 30 gm daily, sometimes both should be tried If the anemia appears to be of a secondary type the use of iron in the form of ferrous sulphate 0 3 gm two or three times a day is advised Leucopenia indicates the trial of pentnucleotides intramuscularly 10 to 40 c c daily although marked improvement under this form of therapy usually has not been demonstrated in these cases

Roentgen Rays—For further stimulation of the blood forming organs the use of roentgen therapy to the long bones and spleen and bone marrow extracts has been suggested Others have used ascorbic acid in moderately large doses with reported success

Diet—The diet should contain nourishing food with an excess of animal fats and a high calcium content Calcium preparations may be given orally as supplements to the diet Intravenous infusions of from 1 000 to 3 000 c c daily of from 5 to 10 per cent glucose in saline are of value Good results from the use of ascorbic acid in daily doses of from 200 to 400 mgm intravenously and orally until a normal vitamin C level is attained have been claimed

Mouth, Nose Throat and Skin Hygiene—Because these patients frequently die of a terminal infection particular attention should be paid to mouth, nose throat and skin hygiene

Phenol

Principal Steps—The case of phenol poisoning encountered in industry usually will differ from that seen in private practice in that the mode of poisoning will be by absorption through the skin or by inhalation in the form of vapor rather than by drinking of the material The most important steps then in the acute case of industrial phenol poisoning will be (1) the removal of all clothing to prevent further absorption (2) *washing of all involved areas on the skin with a 25* per cent solution of either alcohol or glycerin and (3) treatment of shock

Respiratory and Circulatory Measures—The patient should be kept as warm as possible and symptoms of circulatory shock and respiratory depression should be treated by use of the various stimulants mentioned in previous sections For respiratory stimulation the most valuable are inhalations of oxygen with from 5 to 7 per cent carbon dioxide and solutions such as metrazol 0 1 gm camphor in oil 1 to 2 c c caffeine sodium benzoate 0 5 gm intramuscularly or coramine 1 5 c c in

travenously or intramuscularly For the circulatory shock intravenous infusion of 1 000 c c of 10 per cent glucose in distilled water and drugs such as the coramine caffeine or epinephrine hydrochloride ½ to 1 c c of 1 1 000 solution intramuscularly may be used However there is some question concerning the advisability of the use of epinephrine in cases of poisoning The use of digitalis preparations is mentioned frequently in treatment of circulatory shock but seems of very questionable value in this situation

First aid Measures—As first aid measures a quantity of olive oil cod liver oil cottonseed oil castor oil or any other available vegetable oil should be given by mouth as well as egg white Mineral oil affords no protection against phenol since the solubility of phenol in it is quite small about 1 in 50 parts Alcohol previously thought to be of value should not be given by mouth or used for gastric lavage since alcohol although a good solvent for phenol seems to increase the rate of absorption of phenol from the stomach Thorough gastric lavage with 10 per cent solution of glycerin or if this is not available with sodium sulphate 15 gm to the pint of water should be carried out

Nephritis if it occurs as a complication should be treated by the standard methods employed for this disease

It has been shown recently by Meyer[35] that a high protein diet given to rats increased very definitely their resistance to phenol poisoning This observation however probably has no great practical significance in treatment of the poisoning once it has occurred other than to suggest the use of a high protein diet

Nitrobenzene

Immediate Measures—In acute poisoning the contaminated clothing should be removed at once and areas of the skin on which the substance has been spilled should be cleansed with alcohol Gastric lavage with water containing epsom salts which delays absorption is to be performed although as in phenol mercury and arsenic poisoning the lavage is not of as much value in the industrial case as in that of poisoning by ingestion which is more apt to be seen in private practice Oils milk and alcohol should not be given by mouth since they tend to favor absorption

Prevention of Respiratory and Circulatory Failure—Inhalations of carbon dioxide 5 to 7 per cent in oxygen are indicated for respiratory

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Mouth Nose, Throat and Skin Hygiene—Because these patients frequently die of a terminal infection particular attention should be paid to mouth nose throat and skin hygiene

Phenol

Principal Steps—The case of phenol poisoning encountered in industry usually will differ from that seen in private practice in that the mode of poisoning will be by absorption through the skin or by inhalation in the form of vapor rather than by drinking of the material The most important steps then in the acute case of industrial phenol poisoning will be (1) the removal of all clothing to prevent further absorption (2) washing of all involved areas on the skin with a 25 per cent solution of either alcohol or glycerin and (3) treatment of shock

Respiratory and Circulatory Measures—The patient should be kept as warm as possible and symptoms of circulatory shock and respiratory depression should be treated by use of the various stimulants mentioned in previous sections For respiratory stimulation the most valuable are inhalations of oxygen with from 5 to 7 per cent carbon dioxide and solutions such as metrazol 0 1 gm camphor in oil 1 to 2 c c caffeine sodium benzoate 0 5 gm intramuscularly or coramine 1 5 c c in

travenously or intramuscularly For the circulatory shock intravenous infusion of 1 000 c c of 10 per cent glucose in distilled water and drugs such as the coramine caffeine or epinephrine hydrochloride ½ to 1 c c of 1 1 000 solution intramuscularly may be used However there is some question concerning the advisability of the use of epinephrine in cases of poisoning The use of digitalis preparations is mentioned frequently in treatment of circulatory shock but seems of very questionable value in this situation

First aid Measures—As first aid measures a quantity of olive oil cod liver oil cottonseed oil castor oil or any other available vegetable oil should be given by mouth as well as egg white Mineral oil affords no protection against phenol since the solubility of phenol in it is quite small about 1 in 50 parts Alcohol previously thought to be of value should not be given by mouth or used for gastric lavage since alcohol although a good solvent for phenol seems to increase the rate of absorption of phenol from the stomach Thorough gastric lavage with 10 per cent solution of glycerin or if this is not available with sodium sulphate 15 gm to the pint of water should be carried out

Nephritis if it occurs is a complication should be treated by the standard methods employed for this disease

It has been shown recently by Meyer[a] that a high protein diet given to rats increased very definitely their resistance to phenol poisoning This observation however probably has no great practical significance in treatment of the poisoning once it has occurred other than to suggest the use of a high protein diet

Nitrobenzene

Immediate Measures—In acute poisoning the contaminated clothing should be removed at once and areas of the skin on which the substance has been spilled should be cleansed with alcohol Gastric lavage with water containing epsom salts which delays absorption is to be performed although as in phenol mercury and arsenic poisoning the lavage is not of as much value in the industrial case as in that of poisoning by ingestion which is more apt to be seen in private practice Oils milk and alcohol should not be given by mouth since they tend to favor absorption

Prevention of Respiratory and Circulatory Failure—Inhalations of carbon dioxide 5 to 7 per cent in oxygen are indicated for respiratory

stimulation and coramine 1 5 c c metrazol, 0 1 to 0 3 gm caffeine sodium benzoate 0 5 gm or camphor in oil, 1 to 2 c c may be given intramuscularly for respiratory and circulatory stimulation Intravenous infusions of from 5 to 10 per cent glucose in physiological saline solution are indicated and transfusion of blood, 350 to 500 c c, may be necessary If acidosis is present it should be treated as described under Methyl Alcohol Epsom salts 15 to 30 gm usually is to be given orally

Hepatic Injury —Following the acute stage treatment directed at correction of the liver damage may be necessary and this should follow pretty *closely that outlined under Tetrachlorethane If a macrocytic* type of anemia develops liver extract 15 to 30 units per day for the first three or four days and then at intervals of from 5 to 10 days should be given

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XXXIII

DYE INTERMEDIATES AND URINARY BLADDER TUMORS

By John H. Foulger

An unusual incidence of urinary bladder tumors among workers in the German dye industry was first reported by Rehn[1] in 1895. At that time coal tar dyes had been manufactured in Germany for about 35 years. In 1905 Schedler[2] described similar conditions in the Swiss industry. English reports of urinary bladder tumors appeared in 1918 and Russian in 1926. The United States dye industry was established during the latter years of the First World War and bladder tumors in dye workers were not reported until 1931. In other countries (Italy and Japan) a similar time lag has occurred between establishment of the manufacture of dye and the first reporting of an abnormal incidence of urinary bladder tumors.

Workers engaged in the manufacture of dyes may be exposed to a large number of aromatic nitro and amino compounds. Because early dyes were almost entirely aniline derivatives, the terms "aniline bladder tumors" or "aniline dye tumors" have been used to describe this particular occupational disease. These terms are incorrect and should no longer be employed, for careful clinical observation of workers exposed only to aniline has shown that such exposure does not lead to bladder tumors. Further, there is yet no proof that any true aniline dye is carcinogenic for the urinary bladder.

Careful study of the problem to date indicates that only a single compound, beta naphthylamine, is conclusively proved to cause urinary bladder tumors in humans. There is a suspicion that benzidine may be a causative agent, but as yet only a very few cases have been reported in workers exposed to benzidine alone, and the incidence has not yet been proved greater than the incidence of such tumors in workers not exposed to industrial chemicals. Clinical observations on aniline and benzidine are confirmed by animal studies. It is easy to produce a urinary bladder tumor in a dog by feeding beta naphthylamine. Comparable doses of benzidine or of aniline have not produced such tumors in dogs even when fed daily for five years.[3]

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Once papillomata have been detected a worker should receive thorough study and treatment by a urologist properly informed on this particular problem Even though treatment may be successful in removing early growths the worker should be kept under continual observation

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Pure alpha naphthylamine does not produce bladder tumors in experimental dogs but in certain processes for manufacture of the alpha compound there may be contamination with beta naphthylamine In some phases of the operation the beta content of residues may exceed twenty per cent by weight Bladder tumors in workers exposed to crude alpha naphthylamine are therefore probably due to the beta compound

The first sign of injury to the bladder wall which may end in tumor formation is seen through the cystoscope as a localized area of discoloration often with local dilation of blood vessels This grows into a papilloma which at first benign can develop all stages of malignancy Multiple papillomata may occur The removal of a single growth by fulguration or other means does not prevent subsequent growth of other tumors in the bladder Metastases are rare both in humans and animals

The minimal exposure to beta naphthylamine required to produce a tumor is unknown Since the compound can enter the body through both lungs and skin the only adequate protection is a process of manufacture so enclosed and controlled that human exposure is nil This degree of control is not met in most existing manufacturing processes Therefore in addition to limiting the possibility of skin contact with or inhalation of beta naphthylamine workers must be under rigid medical observation based principally upon routine cystoscopic examination All workers required to spend a significant portion of their time in the manufacturing area should be cystoscoped in their selective employment examination and cystoscopy should be repeated at least once a year

Experimental evidence in dogs indicates that once sufficient beta naphthylamine has entered the body to cause minimal injury to the urinary bladder the process of tumor formation will go on even though all exposure is stopped at once For this reason simple removal of a worker from the operation is not adequate to prevent ultimate injury Obviously if there is possibility of exposure to the compound the number of workers in a given operation should be reduced to a minimum

There are no reliable data on the length of time required to produce bladder injury in humans with beta naphthylamine In dogs tumors have been produced in as short a time as six months but usually continuous feeding with the compound for almost two years is necessary

Hundreds of aliphatic and aromatic compounds may be found in the various products refined from crude petroleum the types of compounds being determined by the source of the crude oil and by the refining process The trend in refinery operation is toward the use of conditions that will result in the production of a high proportion of hydrocarbons of the desired commercial type For example in 1941 the total capacity for catalytic cracking in the United States was 200 000 barrels per day Today the capacity is 1 00 000 barrels and still increasing to meet the demand for the olefins and aromatics desired in motor gasolines Increased percentages of olefins are being obtained also from expanded facilities for polymerization of cracked refinery gases by reforming and polyforming These changing methods of manufacture result in continuing change in product In 19 5 for example two thirds of the total gasoline production was straight run and natural consisting mainly of paraffinic hydrocarbons Today paraffinic hydrocarbons make up about 40 per cent of the total in gasoline olefins and aromatics the remainder Distillate type fuels Diesel fuels and domestic burner oils now contain correspondingly increased percentages of olefins and aromatics

Since the physiologic response to the different fractions and compounds in gasoline varies widely the hygienic importance of any changes in refining practice is evident Unsaturated compounds especially the aromatics have marked convulsant effects as compared with the saturated hydrocarbons As a result of the generally lower volatility the aromatics appear to be of lesser toxicologic significance than do the olefins and di olefins Benzol which may be present in small amounts has not been responsible for damage to the hematopoietic system as a result of exposure to gasoline as used in commerce

Petroleum Hazards

The complexity of modern refining practice has been associated with the introduction of a number of toxic chemicals These include such irritants as $AlCl_3$ BF_3 $MgCl_2$ volatile druglike substances such as dichlorodiethylether and a variety of compounds added to products as antioxidants antiknocks and metal deactivators Any of the foregoing may result perhaps in an illness among refinery personnel which requires differentiation and accordingly mention is made

Although it is now generally known that the hydrocarbon content of petroleum products is the agency responsible for intoxication ques

XXXIV

PETROLEUM AND ITS PRODUCTS

By Willard Machle and Emil Beyer

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Composition of Petroleum

Petroleum or crude oil as it comes from the ground is a brownish green to black liquid mixture composed primarily of hydrocarbons. Small amounts of hydrocarbon derivatives containing sulfur, nitrogen or oxygen usually are present in addition to dissolved gases (CH_4, H_2S), water and suspended matter. Crude oil is of little toxicological significance except with respect to dissolved gases: methane, but rarely is responsible for asphyxia; hydrogen sulphide is not infrequently a cause of conjunctival irritation among workers and at times death from rapid paralysis of the respiratory center.

The composition of petroleum has never been completely determined and no two crude oils are exactly alike[1]. Certain broad groups may, however, be differentiated on the basis of dominant pattern of hydrocarbon structure of the components. The classification generally used is paraffinic, naphthenic, mixed and aromatic base. In general paraffinic base oils are found in Appalachian, Michigan and East Texas fields, the naphthenic base in the Gulf Coast, California and South America fields, mixed base oils in the Mid Continent, Canadian and Central European fields and the aromatic oils in parts of California, in Asia and the East Indies.

solvent vapor in air the victim falls in coma and may die at once or within a few hours With exposure to lower concentrations onset of coma is less rapid and there may be initial symptoms simulating alcoholic intoxication incoordination restlessness excitement combativeness confusion disorientation and disturbances of speech Delirium follows and coma lasting for a few hours to several days may ensue In general paraffinic hydrocarbon products produce a relatively quiet type of coma whereas the unsaturated hydrocarbons cause convulsions motor unrest tremors and jactitation Meningismus may be present and in severe cases epileptiform convulsions are frequent at times continuing for days after the coma has passed[5]

Pulse is variable Usually weak and rapid in the early stages of coma it is often full when considerable motor unrest is present Bradycardia has been noted in occasional cases A peripheral vasomotor paralysis is found frequently and apparently is the result of direct action of the agent in the vessels since drug response is abolished There is an associated cyanosis Temperature usually is subnormal except when there is marked unrest There may be terminal hyperpyrexia Respirations usually are shallow and rapid particularly if poisoning has been by ingestion plus aspiration Irregularity of respiration is common and sudden apnea may occur when the patient seems to be doing well

In quiet coma the superficial and deep reflexes are weak or absent but with motor unrest or jactitation they may be greatly increased Plantar reflexes may be reversed Pupils are dilated may be fixed and nystagmoid movements may be present Vomiting and singultus sometimes occur during coma and may persist after coma disappears When there has been aspiration of liquid all of the symptoms of aspiration pneumonia may intervene Fatal pneumonia has been reported following the aspiration of fuel oil[6]

In cases of subacute intoxication general symptoms may not appear for several hours after beginning of exposure although there is irritation of the eyes and throat Premonitory symptoms are headache usually described as a feeling of pressure blurred vision vertigo ataxia tinnitus nausea and anorexia weakness and in some cases general abdominal pain[7] Later there develops a state of intoxication commonly called naphtha jag The sensation may be pleasurable and persons have been known to inhale gasoline vapors intentionally in most cases the patient becomes quarrelsome and combative Whether or not this prodromal period is followed by more serious symptoms depends upon two

tions have been raised concerning the antiknock compound lead tetraethyl. This has been used in gasoline continuously since 1926 in concentrations not exceeding 1 to 1 260 by volume for motor fuel and slightly higher in aviation gasoline. Investigations and reports in the period since 1926 have demonstrated that lead poisoning will not result from the use of leaded gasoline as ordinarily handled in commerce[3]. The hazards are limited to the manufacture of lead tetraethyl and the antiknock mixtures, the mixing of the concentrated "ethyl fluid" with gasoline and the cleaning of tanks in which leaded gasoline has been stored. There are no verified reports of cases of lead poisoning from the commercial handling or use of leaded motor fuels. The possibility must be considered, however, in situations where there is opportunity for accumulation of residues of gasoline that has evaporated, or when leaded gasoline is used as fuel in stoves for heating and cooking.

Etiology

Opportunity for exposure to petroleum and its products is almost general in the population of the United States. In fact the systemic safety and hygienic measures generally in practice within the petroleum industry have now made industrial poisoning a rarity, whereas intoxication, especially that from gasoline, occurs with measurable frequency outside the industry[4]. Usual exposure is to vapors, thus limiting the practical hazard to the lighter solvent mixtures and to gasoline. Though extremely unpleasant and irritating to taste, accidental ingestion of gasoline or kerosene does occur, especially in children. There have been occasional cases in motorists from the syphoning of gasoline. Water from wells that have been contaminated with gasoline infrequently has caused poisoning. There is no conclusive evidence that systemic poisoning from gasoline can be produced in man by cutaneous absorption alone.

Symptoms

Local action is irritant and rubefacient, and severe cutaneous burns may occur if clothing wetted with gasoline is allowed to remain in contact with the skin.

Acute poisoning is characterized by severe central nervous system symptoms. If exposure has been to high concentrations of gasoline or

solvent vapor in air the victim falls in coma and may die at once or within a few hours With exposure to lower concentrations onset of coma is less rapid and there may be initial symptoms simulating alcoholic intoxication incoordination restlessness excitement combativeness confusion disorientation and disturbances of speech Delirium follows and coma lasting for a few hours to several days may ensue In general paraffinic hydrocarbon products produce a relatively quiet type of coma whereas the unsaturated hydrocarbons cause convulsions *motor unrest tremors and jactitation Meningismus may be present* and in severe cases epileptiform convulsions are frequent at times continuing for days after the coma has passed[5]

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factors the intensity and duration of exposure which affect level and degree of equilibrium between vapor in air and blood

The relationship between levels of exposure and physiological effects is not clearly established In general however concentration of gasoline vapor in air in excess of 0 1 per cent by volume is likely to produce serious symptoms within minutes[8] Concentrations in excess of 0 7 per cent by volume will produce definite intoxication in a matter of minutes and concentrations of 1 0 per cent are rapidly fatal for most experimental animals Chronic effects have been established to occur although habituation to low concentrations is the usual phenomenon Repeated exposure to amounts of vapor in air tolerable only to habituated persons has resulted in undernutrition pallor and hypochromic anemia There may be also anorexia nausea irritability headache vertigo and conjunctival irritation Tremors paraesthesias and ataxia have been reported

Sequelae

Acute intoxication may result in sequelae resulting principally from damage to the central nervous system In our experience they are seen most frequently in those cases in which the patient has suffered long periods of coma with convulsions Epileptic attacks are the most serious sequel and may first appear in from 5 to 7 months after the apparent recovery from the acute attack Other common sequelae are peripheral neuritis impairment of memory dullness of intellect, numbness of extremities and cranial nerve palsies

Diagnosis

Acute poisoning does not usually impose difficulty in diagnosis There is history of exposure and the odor of gasoline clings to the clothes and skin If poisoning has been by ingestion both the vomitus and the washings from lavage will have this smell for as long as 3 or 4 days The odor of petroleum distillate can be detected also in the expired air for hours after exposure to high concentrations

There is little characteristic about the patient s general appearance In quiet coma the vasomotor collapse cold extremities and cyanosis may simulate shock In the petroleum industry where men s clothing usually carry some odor of product early diagnosis in unconscious patients

may present difficulty especially so from the differentiation of acute asphyxia resulting from H S and CO intoxication

Prophylaxis

Petroleum products as solvents gasoline kerosene or middle distillate should be considered as being toxic agents In addition to the precautions required by inflammability care should be exercised to prevent access by children Leaded gasoline should be used as a motor fuel only not for cleansing or as a fuel in stoves and heaters Concentration of gasoline vapor in air should be kept below 0 1 per cent and where there is daily exposure below 0 05 per cent by volume No special preemployment or control examinations are needed for workers who may be exposed to the vapors of petroleum products since significant exposures are incidental in nature

Every effort should be made to prevent the contamination of working areas with vapors of hydrocarbons Adequate ventilation should be provided In emergencies and when only short periods of exposure are required airline or self contained respirator equipments must be provided

Prognosis

Most cases of acute intoxication recover without serious after effects or sequelae As in other intoxications prolonged coma convulsions and epileptiform seizures are concomitants of severe illness Since the magnitude of exposure by inhalation usually cannot be determined the prognosis is best based upon the clinical state during the acute episode More definite data are available for poisoning by ingestion Fatality rates in children range from 8 to 50 per cent[9] following ingestion of gasoline These limits may be compared with a rate of 9 0 per cent reported for ingestion of kerosene[8, 9]

Treatment

There is no specific treatment for intoxication with petroleum hydrocarbons If the material has been taken by mouth gastric lavage should be carried out as soon as possible and should be the first treatment

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January 1 1952

instituted even though from 24 to 48 hours may have elapsed since ingestion Petroleum products are absorbed slowly, and lavage tends further to reduce frequency of vomiting[10] If there is no enteritis and diarrhea saline cathartics and enemas should be given to eliminate any ingested material still present in the enteric tract

Embarrassment of respiration is frequent if breathing stops artificial respiration should be instituted using oxygen and carbon dioxide mixture Since much of the volatile hydrocarbon is excreted by way of the lungs the blood concentration can be reduced and the course of the acute illness shortened if adequate pulmonary ventilation is assured by the administration of oxygen and carbon dioxide mixture Unexpected vomiting or failure of respiration is most likely to occur in the first 3 or 4 days of illness accordingly continuous attendance is needed during this time If evidence of failure of peripheral vasomotor control appear heat should be applied and therapy for the collapse instituted Epinephrine should not be used There is good evidence that hydrocarbons may sensitize the myocardium to the effects of epinephrine increasing the danger of ventricular fibrillation Varying degrees of liver damage are usual and may require therapy as guided by functional tests and the state of nutrition during convalescence In chronic cases exhibiting anemia and vague neurologic disturbances the patient usually will recover quickly after removal from exposure especially when on a regimen of regular exercise full diet and anti anemic therapy

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CHAPTER XIX-A

THE EFFECTS OF HEAT

By JEROME W. CONN

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(7) Clinical and biochemical observations during the various types of heat collapse One cannot fully understand the clinical syndromes which may result from exposure to heat without a knowledge of the fundamental physiological mechanisms inherent in man for his protection against such circumstances

(8) Therapeutic measures

Physiological Response of Man to High Environmental Temperatures

Within a very wide range of environmental temperatures man maintains a surprisingly constant internal temperature by virtue of various physiological adjustments which occur reflexly Under all circumstances in which the environmental temperature is equal to or below the skin temperature the internal temperature of the body is dependent upon a balance between two factors namely heat production within the body and heat loss from the body When one equals the other internal temperature remains constant When total heat production exceeds total heat elimination internal temperature rises and the reverse is true when heat loss exceeds heat production When dealing with very high environmental temperatures another factor must be considered If conditions are such that the environmental temperature is higher than the skin temperature heat actually is absorbed by the body from its environment Under these circumstances the mechanisms responsible for heat elimination from the body are pressed In order that internal temperature remain normal they must be capable of eliminating the sum of the two heat loads i e total heat production within the body plus heat absorption from without Thus one must be familiar with the factors contributing to production of heat within the body and with those which are responsible for heat elimination from the body In the final analysis it will be seen that the limit of man s tolerance to heat is dependent upon (1) failure of the heat dissipating mechanisms (either physical or physiological) leading to increased internal temperature or (2) biochemical disturbances secondary to excessive sweating leading to profound disturbances in electrolyte and water metabolism

Heat Production

All of man s potential energy reaches him in the form of food Within him it is converted to kinetic energy which leaves his body in two forms heat and mechanical work Man as a machine is at best only 25 per cent efficient Thus most of the energy expended in the performance of mechanical work manifests itself within the body as heat This heat mechanical heat production plus the heat which is produced under conditions of rest basal metabolic heat production make up total heat production The basal metabolic heat production is fairly constant for the individual The mechanical heat production on the other hand can be varied at will from essentially zero (sleep) to an amount equal to 10 or

INTRODUCTION

Adverse effects of heat upon man have been recognized for centuries. Between 1771 and 1775 several clinical and laboratory reports[1-3] appeared dealing with abnormalities encountered in hot environments. In fact, Jackson[3] emphasized the preventative aspects by propounding a set of rules to govern the mode of life in tropical regions. With the advent of hot industries into modern civilization, ships stokers, miners, blast furnace workers, etc., the problem of heat sickness moved northward. Numerous clinical studies involving large numbers of patients were reported, and there gradually evolved the modern clinical classification of syndromes resulting from exposure to heat, namely, heat stroke, heat exhaustion and heat cramps.

The clinical picture of each of these syndromes is distinct and easily recognizable when observed in its pure form, but considerable overlapping occurs, and in the individual patient elements characteristic of more than one classical type of heat disease may be observed. Management must differ in accordance with the abnormal state which presents itself. Successful therapy, therefore, depends, in a large measure, upon a knowledge of the abnormal physiological processes involved in its production.

Important contributions on the physiological effects of heat upon man have appeared in the past several years. World War II stimulated intensive research in this field because of the need for more information applicable to protection and treatment of fighting men exposed to unaccustomed tropical and desert conditions. Although some of this newer knowledge has not yet been released by governmental agencies, much of it is now available. It should be pointed out that most of the new biochemical and physiological data have been obtained in the laboratory where normal men have been studied under simulated jungle and tropical conditions. However, field studies have, for the most part, confirmed the laboratory findings.

Among the many aspects of man's response to a hot environment, the following have been studied in detail:

(1) Mechanisms involved in the production, absorption and dissipation of heat by the body.

(2) Limits of tolerability to heat both at rest and at work.

(3) Influence of clothing, humidity, radiant energy, availability of water and salt.

(4) Adaptive mechanisms (acclimatization) which occur with continued exposure to heat.

(5) Elements (alcohol, sleeplessness, fatigue, etc.) which interfere with man's ability to cope with a hot environment.

(6) Measures to prevent heat sickness.

(7) Clinical and biochemical observations during the various types of heat collapse One cannot fully understand the clinical syndromes which may result from exposure to heat without a knowledge of the fundamental physiological mechanisms inherent in man for his protection against such circumstances

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Physiological Response of Man to High Environmental Temperatures

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(5) Elements (alcohol sleeplessness fatigue, etc.) which interfere with man s ability to cope with a hot environment

(6) Measures to prevent heat sickness

Under ordinary conditions of comfort 24° C and 20 per cent relative humidity about 80 per cent of the total heat production is removed by the processes of radiation and conduction aided by moving air currents convection and the remaining 20 per cent by the vaporization of water from the surface of the skin and from the lungs The vaporization of a gram of water at 0° C requires 0 586 kilocalories of heat This physical phenomenon accounts for the loss of body heat which accompanies evaporation of water from the body Dill[8] has calculated that one liter of water vaporized at an average skin temperature of 33° C absorbs 580 kilocalories

As the ambient temperature (that which encompasses the body) rises a reflex vasodilatation of the cutaneous vessels occurs This represents an attempt to circulate a greater amount of hot blood through the surface structures to take greater advantage of radiation conduction and convection since ambient temperature still is below skin temperature But as the environmental temperature continues to rise this vascular defense becomes an uphill and losing battle since at an ambient temperature of 36° C the skin temperature reaches about the same level and no further loss of heat by these methods is possible Despite this fact vasodilatation continues[9] and may result in marked pooling of blood peripherally[10] This is in part responsible for some of the cardiovascular manifestations of heat diseases to be discussed below

When the environmental temperature approaches the skin temperature a dramatic physiological adjustment takes place This sharp change occurs when the skin and ambient temperatures reach about 35 C and 32 C respectively It consists of a sudden outpouring by the sweat glands of fluid for evaporation upon the surface of the body At this point the process of vaporization begins to take over the job of disposal of heat This phenomenon is more easily presented in tabular form (Table I)

TABLE I

THE PHENOMENON OF ACTIVE SWEATING (RELATIVE HUMIDITY 20-30%)

Ambient temp C°	Skin temp C	Heat lost by Cond Rad & Conv % of total	Heat lost by Vaporization % of total
24	31 5	80	20
26	32	8	22
28	33 5	72	28
30	34 5	70	30
32	35 5	65	35
34	35 6	40	60
36	35 6	0	100

Critical zone (calculated from data of Winslow and associates[11, 12] and Du Bois[13])

12 times the basal metabolic heat production * It is of course impossible for man to continue at this rate of physical work for any prolonged period of time But even for short periods of time an acute heat load thus produced may overwhelm the capacity of the heat dissipating mechanisms and result in a temporary or prolonged elevation of internal temperature The duration of the fever under these circumstances is a function of the external environment, temperature humidity air movement etc (see Heat Elimination) In a similar way prolonged hard work moderate activity or even complete rest may, depending upon the external environment result in an elevation of internal temperature

When a rise of internal temperature occurs under these or any other circumstances a new increment of heat is produced The basal metabolic heat production, referred to above as being a fairly constant portion of the total heat production increases according to Van t Hoff s law from 30 to 60 per cent for a 3 degree rise (37° to 40° C)[4]

The heat, which is liberated in the processes of metabolism of the various foodstuffs specific dynamic heat represents another source of heat which is of relatively minor importance In the average mixed diet it constitutes an amount of heat equivalent to about 6 per cent of the caloric content of the diet Since protein foods exert a greater specific dynamic effect than the other two foodstuffs it has been suggested that a diet low in protein might be the one of choice for use in hot climates (see Diet)

Heat Elimination

Heat is lost from the body surface in a purely physical way, just as any warm moist inanimate object loses heat to its environment This transfer is accomplished by means of radiation conduction and convection of heat to surrounding elements air and objects and by evaporation of water Man, however, is endowed with a physiological mechanism which enables him within limits to alter automatically the relative proportions of the total heat which is to be lost by the various physical means available to him These physiological adjustments are controlled by various centers within the hypothalamus[5, 6, 7] and constitute the so-called autonomic regulation of body temperature'[6] The constant stimuli to the heat regulating centers of the brain are conditioned by the external environment Instability of the heat regulating center is a constant accompaniment of heat stroke (see under Heat Stroke)

Among the more important peripheral effects, which are mediated via the hypothalamus and which allow man to adjust his means of heat loss are (1) cutaneous vasoconstriction and vasodilatation and (2) active secretion of sweat

* A total 24 hourly metabolism of about 5 000 calories is considered to be in the range of hard physical work This represents a mechanical heat production of roughly 3 300 calories or an amount of heat equal to twice the basal heat production

combined effects of temperature and humidity it becomes a useful guide in predicting the upper limits of man s tolerance to heat Robinson and associates[14] have shown that a wet bulb temperature of 33 0° C begins to approach man s tolerance limit for heat under the following conditions (1) at rest (2) wearing only shorts (3) exposure time 2 to 6 hours They showed for example that under the conditions mentioned above physiological limiting conditions of air temperature and humidity are as follows

Dry Bulb Temp	*Relative Humidity*	*Wet Bulb Temp*
36 C	98	35
50 C	34	33

Activity clothing duration of exposure and air movement thus also become factors in the determination of man s tolerability to a given wet bulb temperature Eichna and associates[15] using 47 minute standard work periods studied men dressed in regulation Army jungle clothing They found that a drop of wet bulb temperature from 90 F to 85 F produced by a fall of humidity from 99 to 94 per cent at a constant dry bulb temperature of 91 F resulted in the following changes in performance indices (1) heart rate decreased from 131 min to 115 min (2) rectal temperature decreased from 100 6 F to 100 F (3) sweating rate decreased from 1 248 gms to 725 gms 47 minute working period

Air movement wind electric fan etc plays an important role in aiding the processes of conduction of heat from the surface of the body and of evaporation of water from the skin provided that ambient temperature is below skin temperature and relative humidity is less than 100 per cent That is thermal and evaporative gradients for these processes are necessary Where these gradients do not exist increase in air motion does not increase heat loss Stagnant air surrounding the body becomes warmer and wetter Air movement aids heat elimination by providing frequent changes of relatively dry for wet air and relatively cool for warm air

Acclimatization to Heat

This phrase denotes certain physiological adjustments or adaptations that gradually develop when man is forced to live and work in an environment which is considerably warmer than that to which he has been accustomed The modus operandi of these physiological changes is only partially understood Many factors known to be involved require further study and there undoubtedly exist many other factors as yet undiscovered Nevertheless the phenomenon is real and easily observable

Dill[3] demonstrated that a 3 week period of residence in the desert resulted in marked improvement of man s ability to perform a given task and that the increase in body temperature obtained was considerably less than it had been

If now the ambient temperature rises above the skin temperature heat is absorbed by the body, and this heat, too must be lost by the process of vaporization if the internal temperature is to remain constant Within limits this can be accomplished but it becomes a function of the rate at which water can be vaporized from the skin surface This rate is in turn dependent upon other factors the two most important of which are (1) relative humidity and (2) air movement

Thus the phenomenon of sweating becomes the last physiological defense of the body for the maintenance of a normal internal temperature It should be pointed out however, that the process of sweating per se is not the whole story A sufficient amount of the sweat produced must be vaporized in order to carry away the required amount of heat Sweat which drips off of the body as fluid, serves no physiological purpose

One may now summarize in tabular form (Table II) the factors involved in heat exchange in man

TABLE II

Sources of Heat	*Losses of Heat*
1 Basal metabolic heat	1 Radiation
a Increased by rise of internal temperature	2 Conduction
2 Mechanical heat production	3 Convection
3 Specific dynamic heat	4 Vaporization of water
4 Absorption of heat from without	a Skin
a Radiation	b Lungs
b Conduction	5 Influence of hypothalamic heat center in regulating physiological processes
c Convection	a Vasomotor
	b Sweat secretion

Humidity and Air Movement

As the saturation of the ambient air increases vaporization from the body decreases until at 100 per cent relative humidity the process ceases entirely If ambient temperature has reached or exceeded skin temperature and relative humidity is maximal no heat can be lost from the body Under these conditions internal temperature must rise rapidly even in the resting subject Indeed Dill[8] calculates that this rise of internal temperature amounts to almost ° C per hour

When a thermometer covered by a wet wick is swung freely, the temperature reading falls provided that the humidity of the atmosphere is less than 100 per cent This occurs by virtue of evaporation of water from the surface of the thermometer and is called the wet bulb reading Since this reading represents the

Water and Sodium Chloride Metabolism

Under conditions of hard work in the heat sweat volume may amount to as much as 1 to 1 5 liters per hour of work at rest it may approach 0 6 liter per hour If the air is dry desert conditions most of the sweat is evaporated aiding greatly in the elimination of heat When the air is moist tropical conditions over 60 per cent of sweat may drip off the body this increment being of no help in ridding the body of heat In either case however dry or moist heat sodium chloride is lost in considerable amounts It thus becomes imperative in order to prevent dehydration and salt depletion and the physical and mental deterioration which rapidly ensues that water and salt be replaced in adequate amounts

Water — It is generally agreed that thirst does not constitute an adequate guide for replacement of these large losses of water Not one of the forty eight men studied by Bean and Eichna[17] drank enough water voluntarily to replace the amounts lost in the sweat Under these conditions the effects of dehydration soon appeared On the other hand Pitts and associates[9] found that hourly replacement of water in an amount equal to the sweat loss for the period produced the best results with regard to performance of work Restriction of fluid does not decrease sweat volume under conditions of work in the heat[15] nor does sweat volume increase as a result of the ingestion of extra water[9] Deterioration in the heat from lack of water intake is rapid and results in peripheral vascular collapse (see Heat Exhaustion)

Sodium Chloride — Man unacclimatized to heat secretes sweat which contains about 4 grams of sodium chloride per liter There is considerable variation in this regard among individuals and in the same individual at different times The author has found values for different individuals to range from to 8 grams per liter of sweat Season of the year degree of activity and sodium chloride intake are factors which contribute to any given value It is common for men working in the heat to produce 10 or more liters of sweat daily It is thus clear that it is possible to lose from 20 to 80 grams of sodium chloride in the sweat during a 24 hour period So far as is known sodium chloride in the sweat serves no useful purpose and therefore constitutes a paradox to the rule of physiological economy Since the average individual obtains 10 to 12 grams of sodium chloride daily from his diet a sodium chloride loss of 40 grams per day contained in sweat cannot be long continued before profound symptoms of salt deficiency become manifest (see Heat Exhaustion also Heat Cramps)

An interesting mechanism however has been described recently[5] by which the sweat glands practice salt economy It had been demonstrated earlier[1] that as the process of acclimatization to heat progresses the concentration of sodium chloride of the sweat decreases The fully acclimatized individual secretes sweat containing about 50 per cent less sodium chloride per liter than he did before

initially. Bazett and his co-workers[16, 17] showed that men working in hot environments maintain an increased blood and interstitial fluid volume and show a temporary increase in resting cardiac output and an increased peripheral circulation.

The unacclimatized man forced to work in the heat imposes a great burden upon his circulation. The skin demands an increased blood supply to serve the purposes of heat elimination. Adolph[15] estimates that about 2.5 liters of blood per minute must be circulated through the skin in order to eliminate the heat load produced by walking in the desert. Results of this acute diversion of blood to the periphery are early signs of peripheral vascular collapse, namely, rapid pulse rate[19], a decreased stroke volume and sometimes, a decreased minute output[20], severe postural hypotension[9, 21] and peripheral evidence of vascular engorgement[15], flushing of face, neck and chest, injection of sclerae and edema of nasal mucous membranes and often, edema of the hands and feet. Taylor and associates[20] believe that the cardiovascular adjustment which occurs in an unacclimatized man during his first 4 days of exposure to work in the heat and which allows him to overcome these untoward effects consists of a vasomotor adaptation to these new circumstances. They feel that the ability of the acclimatized man to work at a lower level of internal temperature is a result of the improved peripheral circulation.

Other adaptive changes have been observed during the process of acclimatization. The rate of sweating increases as acclimatization proceeds[15, 22, 23]. The sodium chloride concentration of the sweat diminishes[4]. In fact, the sweat glands are capable of affecting a 10 to 15 fold decrease in salt loss from the skin[25] (see under Sodium Chloride Metabolism). Robinson and associates[6] found that pure bred negroes fully acclimatized to humid heat were capable of better performance than white men similarly acclimatized.

Regardless of the mechanisms involved, the results of acclimatization are dramatic. Whereas on the first day of exposure to heat a subject attempting to complete a given work load collapses with high rectal temperature and evidence of peripheral vascular failure, the same individual on the 4th and 5th day of exposure performs the task easily without an unstable vascular system and with a much lower rectal temperature. Most of the improvement is attained during the first 3 or 4 days, but adaptation continues at a slower rate and usually is complete 10 to 14 days after the initial exposure. Simple exposure to a hot environment confers a degree of acclimatization, but a daily short period of work in the heat leads to full acclimatization. Acclimatization to dry heat induces a substantial degree of acclimatization to humid heat[7] and vice versa[15]. Acclimatization persists in diminishing degree for several weeks after removal from the hot environment. If the new environment is warm, acclimatization persists for a longer time than when it is cool[15].

tropical and desert conditions They concluded that within this range of protein intake no significant differences in physical performance could be detected The subjects preferred the high protein diet

Carbohydrate — Although claims have been made that high carbohydrate feeding is of value in protecting against heat exhaustion the results of more recent experiments[33, 34] do not justify this stand

Vitamins — Because of the possibility that significant quantities of the water soluble vitamins might be lost in the sweat and that an increased dietary requirement might thus result this problem has been studied extensively[35 to 41] There is of course considerable doubt that the results of such studies obtained in rats[35, 39] can be applied in man and no comment will be made regarding the discrepancies reported for the two species Mickelsen and Keys[36] have shown that *thiamine and riboflavin are either absent from human sweat or appear in* insignificant amounts and that nicotinic acid is present in small amounts not exceeding 0 1 mgm per 100 c c

Ascorbic acid once believed to be lost in large quantities in sweat and recently advocated for prophylaxis and treatment of heat exhaustion[40] is now found to be present in sweat in negligible amounts[36] The substance formerly believed to be ascorbic acid in sweat has been shown to be a non specific reducing substance which is not attacked by the specific ascorbic acid-oxidase[37] Large supplements of ascorbic acid in the diet do not affect the ability of men to perform hard work in the heat nor do they affect the incidence of heat exhaustion[41]

It is estimated[38] *that the maximal loss of vitamins associated with a production* of 10 liters of sweat daily would be less than 10 mgm of ascorbic and nicotinic acids and less than 50 micrograms of thiamine

Mills and associates[1] reports that rats on a vitamin K deficient diet showed a four fold greater incidence of internal hemorrhage when kept at 90 F than when living at 68 F No parallel findings are available for humans but the possibility should be kept in mind especially where biliary or hepatic disease is encountered in individuals residing or working in hot environments

Factors Known to Decrease Tolerance to Heat

Lack of Acclimatization — (see Acclimatization)

Alcohol — For years it has been recognized that acute bouts of alcoholism lead to increased susceptability to the ill effects of heat[42-47] Talbott[48] felt that the lack of salt intake associated with alcoholic bouts probably was responsible for the increased incidence of heat cramps noted under these circumstances Ferris and associates[49] found that ingestion of alcohol was an important predisposing factor in the precipitation of heat stroke Since alcohol has been shown to stimulate the sweating mechanism[50] depress vasomotor reflexes[51, 52] and

acclimatization, approximately 4 gms per liter to 2 gms per liter, with the same total sweat volume Using fully acclimatized men as subjects, we[5] were able to demonstrate a further adaptability of the sweat glands whereby a concentration of about 0 3 gm of NaCl per liter of sweat could be consistently attained by almost all subjects This mechanism is not activated until the need to conserve body salt becomes acute Under these circumstances the loss of 10 liters of sweat per day entails a loss of only 3 grams of salt as compared with the 20 to 80 gms lost by the unacclimatized man This sharp fall in the concentration of sweat sodium chloride is preceded by one or two days by a sharp fall in the urinary excretion of NaCl to levels approaching zero loss in 24 hours but is accompanied by no significant change in the blood levels of sodium and chloride This mechanism allows men to remain in NaCl balance and to continue to perform hard work in the heat with large sweat volumes, even though the intake of salt is reduced to below 5 grams per day At the time that renal and sweat losses of sodium chloride are falling sharply, there occurs a temporary period of negative nitrogen balance These associated metabolic adjustments strongly suggest that the whole phenomenon is the result of adrenal cortical stimulation[73] It probably represents another example of the so-called alarm reaction' of Selye[30 31] In a recent study by Ladell[32] it was shown that the parenteral administration of desoxy corticosterone acetate produced a 30 per cent decrease in the sodium chloride content of sweat

The conclusion[5] is justified that in fully acclimatized individuals performing hard work in humid heat an average intake of 10 to 15 grams of NaCl daily is sufficient to maintain salt balance and that salt supplements above this level are unnecessary and under some circumstances may be harmful

It must be emphasized however that the unacclimatized individual is incapable of bringing about this adjustment with sufficient rapidity to prevent salt depletion and its consequent symptoms (see Heat Exhaustion and Heat Cramps)

Diet

Man living and or working in a hot environment should receive a sufficient number of calories for maintenance of body weight There is no convincing evidence at present however that the dietary mixture supplying these calories relative amounts of protein fat and carbohydrate is important with regard to his ability to acclimatize to heat or to continue to work in the heat

Protein —Since the specific dynamic heat (see Heat Production) associated with the metabolism of protein is relatively high it has been suggested that a diet low in this foodstuff would lighten the already great burden placed upon the heat dissipating mechanisms Pitts Consolazio and Johnson[33] used high (150 grams) and low' (75 grams) protein diets in men performing hard work under both

of these manifestations namely heat stroke heat exhaustion and heat cramps However it must be emphasized again that this division is arbitrary Although it is not uncommon to encounter a patient who fits precisely into one of the three groupings it is becoming increasingly clear that certain manifestations which usually place the patient in one category may be seen in association with those of another group In fact it is likely that the various types of heat disease which have been described represent (1) varying degrees of the same illness and (2) varying responses to the same insult depending upon the other circumstances under which the primary insult is applied Successful therapy therefore is dependent upon an understanding of the mode of production of each manifestation rather than upon the application of a fixed program of treatment for each of the three groups Expressed differently the fact that a patient satisfies the diagnostic criteria for one group more completely than for another does not alter the necessity for treating all of the manifestations of heat disease For example a man who has been sweating profusely for several days may be on the verge of heat exhaustion from the peripheral vascular collapse which is associated with the loss of excessive amounts of salt and water At this point he may suddenly stop sweating The internal temperature then may rise rapidly the skin become hot and dry and the presenting picture of heat stroke overshadow the associated abnormality Such a patient might well die in shock during the time that efforts are directed toward reducing internal temperature unless measures designed to increase blood volume and cardiac stroke-output are carried out simultaneously

Heat Stroke
(Sun-Stroke Heat Hyperpyrexia Thermic Fever)

Mechanism — Under any circumstances in which the total heat production within the body plus that which is absorbed from the environment exceeds that amount which is dissipated from the body (see Heat Production and Heat Elimination) the temperature of the body rises Depending upon the duration of these circumstances the total unexpended heat load may result in the production of an internal temperature as high as 112 F When the internal temperature rises above 106 to 107 F a condition of stupor ensues followed shortly thereafter by deep coma Thus an effect of the elevated temperature upon the central nervous system soon becomes evident

Characteristic of the patient who has developed heat stroke is the instability of his heat regulatory mechanisms Temporarily at least the heat regulating center located in the hypothalamus[5, 6, 7] becomes extremely deficient in its functions Whether this functional aberration in the hypothalmus is the result of the elevated temperature of the brain or the cause of the breakdown of temperature regulation leading to hyperpyrexia still remains an open question

Under ordinary conditions of life in a temperate climate by far the majority

produce vasodilatation of peripheral blood vessels[5, 53], it seems likely that these pharmacological effects of alcohol are responsible for increasing the morbid effects of heat. Eichna and associates[15] have shown recently that "the hangover of alcoholic intoxication impairs work performance in the heat the next day." Fully acclimatized men whose daily work performance was known, were given sufficient whiskey to become markedly intoxicated within a two hour period. The next morning it was found that the usual amount of work produced (1) a greater sweat volume, (2) a more rapid heart rate and (3) a higher rectal temperature. By afternoon, however, their performance had returned to normal.

Lack of Sleep.—All observers are in agreement that one or two nights of restlessness with lack of sleep results in a marked deterioration of physical performance in the heat. The effect is much more profound in hot environments than in temperate ones.

Clothing.—When the environmental temperature is high and most of the heat dissipated from the body is by way of evaporation of water from the skin or through the clothing, the latter becomes a handicap except under one of two conditions. First, the body absorbs radiant energy from the sun and under conditions of exposure to sunlight much of this energy may be deflected, the infrared rays being of particular importance, by covering exposed surfaces with clothing. Secondly, intermittent blasts of heat as from a blast furnace may be partially deflected from the body by clothing. When clothing is worn, wet clothing is more advantageous than dry clothing[15, 54] producing a lower working pulse rate, rectal temperature and sweating rate.

Lack of Salt and Water.—(see Water and Sodium Chloride Metabolism).

Physical Fitness.—Lack of physical training for work to be performed in the heat constitutes an important cause for collapse. Illnesses of all kinds but particularly febrile illnesses and those associated with vomiting or diarrhea produce rapid deterioration of performance and lead to the various forms of heat disease.

Age.—During a heat wave in a temperate climate by far the great majority of individuals who suffer heat stroke are people of middle life or beyond. Ferris and associates[49] studying a group of 44 patients with heat stroke found all but 7 to be past 50 years of age, the greatest frequency occurring between 60 and 70. They found likewise, of course, that the incidence of degenerative diseases associated with senility were high in the group studied. Since the heat load observed in these elderly patients was not the result of work in the heat, they suggest that the mechanisms for the dissipation of heat are less effective in elderly than in young people.

Heat Disease

For the sake of clarity of presentation the various clinical manifestations of heat disease will be grouped according to the commonly accepted classification.

of these manifestations, namely, heat stroke, heat exhaustion and heat cramps. However, it must be emphasized again that this division is arbitrary. Although it is not uncommon to encounter a patient who fits precisely into one of the three groupings, it is becoming increasingly clear that certain manifestations which usually place the patient in one category may be seen in association with those of another group. In fact, it is likely that the various types of heat disease which have been described represent (1) varying degrees of the same illness and (2) varying responses to the same insult depending upon the other circumstances under which the primary insult is applied. Successful therapy, therefore, is dependent upon an understanding of the mode of production of each manifestation rather than upon the application of a fixed program of treatment for each of the three groups. Expressed differently, the fact that a patient satisfies the diagnostic criteria for one group more completely than for another does not alter the necessity for treating all of the manifestations of heat disease. For example, a man who has been sweating profusely for several days may be on the verge of heat exhaustion from the peripheral vascular collapse which is associated with the loss of excessive amounts of salt and water. At this point he may suddenly stop sweating. The internal temperature then may rise rapidly, the skin become hot and dry and the presenting picture of heat stroke overshadow the associated abnormality. Such a patient might well die in shock during the time that efforts are directed toward reducing internal temperature unless measures designed to increase blood volume and cardiac stroke output are carried out simultaneously.

Heat Stroke

(Sun Stroke, Heat Hyperpyrexia, Thermic Fever)

Mechanism.—Under any circumstances in which the total heat production within the body plus that which is absorbed from the environment exceeds that amount which is dissipated from the body (see Heat Production and Heat Elimination) the temperature of the body rises. Depending upon the duration of these circumstances the total unexpended heat load may result in the production of an internal temperature as high as 112° F. When the internal temperature rises above 106° to 107° F. a condition of stupor ensues followed shortly thereafter by deep coma. Thus an effect of the elevated temperature upon the central nervous system soon becomes evident.

Characteristic of the patient who has developed heat stroke is the instability of his heat regulatory mechanisms. Temporarily, at least, the heat regulating center located in the hypothalamus[5, 6, 7] becomes extremely deficient in its functions. Whether this functional aberration in the hypothalmus is the result of the elevated temperature of the brain or the cause of the breakdown of temperature regulation leading to hyperpyrexia still remains an open question.

Under ordinary conditions of life in a temperate climate by far the majority

of patients who develop heat stroke during a siege of hot weather are people past the age of 60 years[40, 54] Pathognomonic of this type of heat disease is the sudden cessation of sweating shortly before the onset of the collapse syndrome It is for these reasons advanced age associated with cerebral arteriosclerosis and cessation of sweating before collapse, that some believe that the elderly 'autonomic regulator of body temperature hypothalamic becomes insufficient under conditions of great stress and that the breakdown of the peripheral mechanisms for heat dissipation resulting in marked hyperpyrexia is a secondary phenomenon

It is significant that the incidence of heat stroke closely parallels the duration of the heat wave Few cases are observed during the first 2 days, but after 4 days the incidence begins to climb rapidly When nights are cool the daytime accumulation of heat is dissipated A continuously hot environment is a prerequisite for the development of heat stroke This is not necessarily so in the case of heat exhaustion or heat cramps

Symptoms and Signs — Heat stroke usually manifests itself as a sudden collapse associated with stupor or deep coma but frequently prodromal symptoms have been experienced or may be complained of before the stroke occurs The following are common prodromal symptoms which may be noticed for as long as 2 or 3 days They should be classified as symptoms associated with mild heat retention the term heat stroke being reserved for the sudden loss of consciousness that accompanies severe heat retention

Weakness
Dizziness
Attacks of fainting
Nausea and vomiting
Headache
Insomnia
Excessive warmth (rectal temp below 106° F)
Sudden cessation of sweating (shortly before the stroke)
Great excitement and emotional instability (shortly before the stroke)

The clinical picture of full blown heat stroke follows

Profound coma with or without convulsions
Rectal temperature — 106 to 11 F
Skin — Dry hot and red absence of sweating often petechial hemorrhages
Respirations — Rapid and deep (Kussmaul in type)
Pulse — Full bounding and rapid (100 to 160 per min)
Blood pressure — Mild systolic elevation with wide pulse pressure $\frac{140}{50}$ to $\frac{170}{80}$
Tendon reflexes — diminished
Muscular flaccidity
Frequently pulmonary basal rales but usually evidence of congestive cardiac failure is absent

The Clinical Course of Heat Stroke — As the condition becomes progressively worse respirations become shallow and irregular blood pressure falls and the pulse becomes more rapid and weak The patient may then die in a shock like state the exceptions to the usual shock picture being that the skin remains dry and the internal temperature elevated

The instability of the heat regulating mechanisms which is characteristic of heat stroke greatly influences the clinical course of the disease It is first noted that removal of the patient to a cooler environment does not result in a significant decrease in body temperature Under treatment (see that section on a subsequent page) for reduction of body temperature it is found frequently that the temperature continues to fall to subnormal levels despite the fact that the measures instituted to initiate cooling were discontinued sometime previously After body temperature has been reduced by treatment, multiple recurrences of fever may occur for many days Sweating may continue to be absent for several days following the stroke even though body temperature has been successfully reduced The heat regulating center may remain extremely labile for many weeks In fact one attack of heat stroke makes the individual more susceptible to subsequent attacks suggesting that the heat regulating mechanisms have sustained permanent injury

Laboratory Data — Heat stroke unless associated with either heat exhaustion or heat cramps is not accompanied by marked alterations in the chemical or cellular components of the blood[9, 49, 56, 67] A mild degree of hemoconcentration is indicated by a slightly elevated level of serum protein and hematocrit values and of the red and white blood cell counts Sodium and chloride levels usually are within the normal range Blood non protein nitrogen may be mildly elevated and CO_2 combining power somewhat reduced Oxygen content of arterial blood is normal Blood sugar is normal Clotting time has been found to be normal even in those patients exhibiting cutaneous petechiae Epinephrine may increase the purpura[56] suggesting capillary damage as the original cause Venous pressure and peripheral blood flow are essentially normal

The urine likewise is of no diagnostic value Occasionally albuminuria and cylindruria are found and the chloride concentration of the urine may be low

Pathology — Little has been added to the well established pathological findings observed in cases that have died in heat stroke [8] The findings common to most cases are edema of the brain and lungs with petechial hemorrhages in both organs Many cases show intracutaneous petechial hemorrhages particularly over the arms and trunk The widespread oc urrence of petechiae in some cases suggests a generalized increase in capillary fragility Such hemorrhages have been observed in the peritoneum intestinal mucosa subserous regions of the large intestine and kidneys In addition subendocardial hemorrhages of the inter ventricular septum involving the conduction system were found in all of a series of 3 cases[59] Although petechiae in the central nervous system are common no

specific lesion of the hypothalamus, thermal regulating center, has been demonstrated

Treatment —In the treatment of heat stroke the immediate and primary objective is to lower body temperature Since time is an important factor the procedure, which lowers body temperature most rapidly is the one of choice providing that the maneuver per se is not injurious Various procedures have been employed

(1) *Removal of the patient to a cool environment* When this is possible it should be done but other methods for rapid cooling must be instituted simultaneously The lability of the heat regulating center and the long period of time required to dissipate the heat load in the absence of sweating make dependence upon this procedure extremely precarious Clothing should be removed at once unless continued exposure to sunlight remains a temporary factor

(2) *Immersion of the patient in ice water* This appears to be the procedure of choice for rapid cooling In the past objections raised to this mode of therapy have been (1) that the procedure is capable of producing shock and (2) that marked cooling of the skin produces cutaneous vasoconstriction[56,60,61] thereby pooling hot blood in the deep tissues of the body and actually preventing effective cutaneous cooling of blood Careful observations in actual practice however fail to support these objections In a series of 25 patients severely ill with heat stroke no instance of shock or cutaneous vasoconstriction was observed as a result of this procedure[49] Only 9 to 40 minutes of immersion was needed to bring body temperature to below 102° F

When immersion in cold water is used with or without ice, vigorous massage of the extremities is of great value in (1) increasing circulation through the skin and (2) in stirring the water so that the fluid being warmed close to the skin is constantly changed It is extremely important that the patient be removed from the tub of cold water when the rectal temperature has been reduced to 10 ° or 103° F After removal from the cold water the temperature is likely to continue to fall 3 or 4 degrees or even more Acute circulatory collapse may occur when the rectal temperature approaches 94° F If the temperature begins to fall to subnormal levels it is advisable cautiously to warm the patient with hot water bottles blankets etc taking rectal temperature readings every 10 minutes Because of the lability of heat regulating mechanisms it may take many hours to stabilize body temperature at or near normal Recurrences of fever (10 ° to 103° F) are very common over the following few days but do not require the heroic therapy outlined above They are easily controlled by increasing evaporative cooling from the surface of the skin

(3) *Increasing evaporative cooling* For patients with prodromal symptoms and relatively mild heat retention rectal temperature below 106° F ice water tubbing is not necessary Such patients respond well to one of various methods of increas

ing vaporization of water from the body surface Probably the most effective method is to cover the nude body with wet sheets upon which one or several electric fans are directed In the field where such things are not available frequent sprinkling of the entire body with water and continuous manual fanning constitute an effective method Where the humidity is very high fanning will not significantly increase vaporization of water In this case immersion of the patient in cool water or the frequent pouring of large amounts of cool water on the body are effective in reducing body temperature

As the patient s temperature falls from extremely high levels to about 107 F, he loses his muscular flaccidity and may either become conscious or become maniacally uncontrollable The question of sedation then becomes important

(4) *Sedation* Sedative drugs may disturb further the function of the heat regulating center and are contraindicated except to control convulsions In this situation sodium pentothal intravenously is the drug of choice Otherwise mechanical restraint is the safest procedure Morphine or adrenalin should not be administered

(5) *General measures* Fluids sufficient to maintain water balance and to overcome the moderate dehydration are needed 3 000 c c daily of a mixture of normal saline and 5 per cent glucose parenterally is adequate and should be given cautiously if signs of pulmonary edema are prominent When the patient can drink oral administration is preferable Blood plasma probably is not indicated in uncomplicated heat stroke Borden s[59] success with its use is due to the fact that his patients were in addition suffering from heat exhaustion and low blood volume Oxygen is indicated in the presence of clinical signs of anoxemia but otherwise is of little value Venesection advocated by some may be indicated by the presence of pulmonary edema and a high *venous pressure* but in general it should be stricken from the list of procedures used in the treatment of any type of heat disease

Prognosis and Sequelae — Comparative mortality statistics for heat stroke which range from 30 per cent to 75 per cent are difficult to evaluate for several reasons (1) the method of treatment has been extremely variable (2) the definition of heat stroke has been interpreted loosely (3) cases of hyperpyrexia complicated by heat exhaustion have been included and (4) consideration frequently has not been given to the average age of the group and to the co-existence of other diseases In the group well treated by Ferris and associates[49] several points stand out The average age was over 60 years and the disease was not complicated by heat exhaustion No patient whose admission temperature was below 107 F died (13 patients — temp range 104 to 107 C) Of the 25 classified as severely ill and satisfying the clinical criteria for heat stroke (temp 106 to 112 F) 8 died giving a mortality rate of 32 per cent It is probable that a large group of younger individuals similarly treated would yield a lower figure

The longer the duration of hyperpyrexia the worse the prognosis An initial temperature above 109° F makes the outlook poor but is not necessarily fatal For patients still alive 48 hours after the initial reduction of temperature the prognosis for life is good

Having suffered an attack of heat stroke, the patient frequently shows an *increased susceptibility* to subsequent attacks under conditions which may be milder than those that produced the initial one This suggests a permanent lesion at least functional in the hypothalamus In fact all of the complications that may occur as the result of heat stroke relate to abnormal function of the nervous system persistent or periodic headache, emotional instability psychoses, paralyses of extremities and involvement of cranial and peripheral nerves The most common sequelae however are increased susceptibility to heat and periodic headache The prognosis in heat stroke therefore must take into account not only the immediate threat to life but also the sequelae which may exist in the surviving patient

Heat Exhaustion
(*Heat Prostration Heat Collapse*)

Of all of the adverse effects of heat known to occur in man the syndrome of heat exhaustion is the most common Unlike most cases of heat stroke heat exhaustion usually is the result of a combination of hard physical work and exposure to heat Although it may occur at any age it is most common during the active, working years of life age 18 to 40 and it is encountered rarely in women Its clinical recognition is easy treatment simple, therapeutic response dramatic prognosis excellent and sequelae absent

Mechanism —The syndrome is essentially one of peripheral vascular insufficiency It is the result of an unreplaced loss of large amounts of salt and water from the body consequent to long continued profuse sweating (see Salt and Water Metabolism) The extracellular fluid volume plasma volume and interstitial fluid volume is critically diminished Biochemically and clinically the picture is akin to that seen in acute Addisonian crisis adrenal cortical insufficiency, but one important mechanistic difference must be emphasized In both conditions heat exhaustion and Addisonian crisis there exists a significant diminution of extracellular fluid volume and of the sodium chloride reserve In the case of heat exhaustion however an additional factor contributes greatly to the acute cardiovascular collapse This consists of the peripheral vasodilation brought about by continued exposure to heat an attempt to dissipate more heat from the surface of the skin This diversion of blood to the periphery in the presence of an already diminished blood volume results in a greatly lessened return of blood to the heart a marked increase in pulse rate (an effort to maintain minute cardiac

output) and finally circulatory collapse When collapse finally occurs peripheral vasoconstriction follows and the clinical picture outlined below appears

Men fully acclimatized to working in the heat are very much less susceptible to heat exhaustion than unacclimatized ones unless their tolerance to heat is impaired by alcohol sleeplessness sickness etc (see Acclimatization and Tolerance to Heat) Acclimatized men who by virtue of their adaptations are successful in warding off symptoms of heat exhaustion and who continue to work in an environment which approaches man s tolerance limit for heat (see under Humidity and Air Movement) develop heat retention or full blown heat stroke Heat stroke developed in this manner is likely to be accompanied by a degree of water and salt depletion heat exhaustion This represents an example of the combined effects of heat stroke and heat exhaustion which may tend to confuse the clinical picture Such a patient may die in shock if the clinical findings are not correctly analyzed and if appropriate therapy is not instituted

Symptoms and Signs — Loss of body salt and water usually go hand in hand giving rise eventually to the typical syndrome of heat exhaustion It is possible, however to develop symptoms from lack of salt alone where water replacement has been sufficient to prevent a severe degree of accompanying dehydration ✓ Such symptoms consist of weakness marked ease of fatigue impaired physical performance and mental acuity anorexia and nausea[6] Pulse rate and blood pressure remain within normal limits

Heat exhaustion combines these symptoms with those of severe dehydration. The clinical picture is as follows

Symptoms

- Weakness
- Marked ease of fatigue
- Anorexia
- Nausea and vomiting
- Mental apathy
- Headache
- Vertigo (especially when erect)
- Fainting in the erect position (relief on recumbancy)
- Visual disturbances
- Dyspnea
- Abdominal cramps

Signs

- Staring anxious glazed expression
- Cold clammy wet skin
- Pallor (sometimes flushing of face and neck)
- Rapid pulse (150 – 200/min)

Signs

(Continued)

Blood pressure — normal or moderately low on recumbency
Marked postural hypotension
Dilated pupils
Mildly elevated rectal temperature (101 F)
Lack of physical coordination
Collapse

Laboratory Data — Hemoconcentration is a characteristic finding in heat exhaustion The red and white blood cell counts usually are elevated The hematocrit reading indicates loss of plasma and the concentration of serum proteins is increased Occasionally a polymorphonuclear leucocytosis as high as 18 000 is encountered In experimental heat exhaustion Taylor and associates[63] report an actual fall in the hemoglobin concentration of the blood in association with a 15 per cent increase in total plasma solids They suggest the possibility of blood destruction as the cause of this phenomenon The plasma chloride concentration is diminished even in the presence of hemoconcentration This represents a severe loss of total blood chloride The blood urea nitrogen usually is elevated but this finding does not indicate a renal lesion Increased protein destruction together with decreased glomerular filtration extra renal azotemia explain this abnormality

The urine is small in amount, highly concentrated and low in chlorides In fact in some cases the urine is essentially chloride free

Treatment — Management of the patient suffering from heat exhaustion is simple and the therapeutic response is rapid He should be removed from the heat when possible Elevation of the legs tends to promote more rapid return of blood to the heart as does massage of the extremities The administration of sodium chloride and water however constitutes the most essential part of treatment If the patient can swallow and retain it he should be given salt water in large quantities to drink A concentration of 0 1 per cent has been recommended[64] because it does not produce gastric irritative symptoms nor have a perceptibly saline taste A very large volume however is required in order to provide a significant amount of salt We have found that higher concentrations up to 1 per cent are well tolerated in heat exhaustion In severe cases physiological saline given intravenously 2 000 to 3 000 c c is sufficient to produce dramatic improvement Mild asthenia may persist for 1 or 2 days but complete recovery within 24 hours is the rule In a series of 437 cases reported from the Bethlehem Steel Company[65] there were no fatalities average treatment time in the infirmary was 2 hours and 36 minutes after which the patient was sent home Many returned to full time duty the next morning For the most severe group the average loss of time from work was 1 77 days per man

Prevention — Heat exhaustion is preventable by replacement of salt and water as they are lost during long periods of excessive sweating. Lack of or loss of acclimatization to heat, alcohol, sickness, etc increase markedly the susceptibility to heat exhaustion. A fully acclimatized man sweating at the rate of 6 to 9 liters per day is able to maintain sodium chloride balance on an intake of 10 to 15 grams daily; this is an average dietary intake. However an individual newly exposed to hard work in the heat requires large amounts of salt and water to prevent heat exhaustion. The process of adaptation requires 10 to 14 days during which time the sodium chloride concentration of the sweat diminishes remarkably. Acclimatization may be lost by a vacation from a hot job, an alcoholic bout, illness, lack of rest at night, etc.

The incidence of heat exhaustion in hot industries has been greatly lowered by making available to the workers salt in various forms. Salinized drinking water probably is the best insurance that the men will take the salt during the working hours of the day. A study from the Inland Steel Company[66] in which a section of steel workers (3,000 men) were given salinized drinking water (0.1 per cent) showed good results as compared with the control group. However some cases of heat exhaustion still occurred in that section, usually among men returning to work after a temporary lay-off. This means that unacclimatized men require more salt than is provided in this way. They should have either more salt in the drinking water or ingestion of salt tablets should be insured. Four grams of salt per hour of work may be needed in the more susceptible cases. Uncoated salt pills may cause gastric distress, nausea and vomiting. Enteric coated salt tablets are quite satisfactory but much more expensive.

Since thirst is frequently a poor index of dehydration, particularly in the presence of salt depletion, the men should be encouraged to drink freely and frequently.

Heat Cramps

Heat cramps consist of excruciatingly painful spasms of voluntary muscles which occur in individuals performing hard physical work in a hot environment. This is frequently, although not always, accompanied by the syndrome of heat exhaustion.

Mechanism — The complete pathogenesis of heat cramps remains puzzling. There is little question that the phenomenon is conditioned by and associated with a low level of sodium chloride in the blood and interstitial fluid and that it can be relieved very promptly by the administration of salt. Thus nothing of significance with respect to the mechanism of production of heat cramps has been added to Talbott's excellent monograph[48] on the subject, but that other factors are also involved seems clear. The following points are significant: (1) most muscles of the body escape spasm; those that become involved are the

ones that are or have been subjected to severe physical strain usually those of the extremities and abdominal wall (2) patients with adrenal insufficiency having similarly low sodium chloride levels do not experience muscle cramps (3) in experimental heat exhaustion, where plasma chlorides dropped below the critical levels established by Talbott[43] no instance of heat cramps was observed[63] It is likely that the threshold for this type of muscle spasm is lowered by interstitial salt deficiency but that the fundamental mechanism involves another metabolic aberration within the muscle which is related to intense muscular contraction

Symptoms and Signs — Many patients who have had several attacks of heat cramps think that they can predict the imminence of an attack on the basis of prodromal symptoms These may begin several hours or several days before the spasms develop and consist primarily of gastrointestinal symptoms, anorexia, nausea, vomiting and diarrhea The symptoms suggest salt deficiency

The onset of cramps usually is abrupt and dramatic The patient is in agony because of intense pain but in mild cases symptoms may come on gradually, be less painful and involve relatively few muscles In most cases the attack begins while the individual is working in the heat but very frequently it occurs several hours after he has returned home from his hot job Often it is precipitated by a cold shower Cold water or cold air directed over a susceptible muscle often will initiate a spasm of that muscle[67]

Symptom and Signs

Agonizing pain in the affected muscles
Periodic spasm of the affected muscles most commonly those of shoulder flexors of the forearm calf muscles abdominal wall and fingers
Respiratory difficulty when muscles of the chest are involved
Vomiting most frequent when the muscles of the abdominal wall are involved
Skin — pale and wet with profuse perspiration
Pupils often widely dilated but this is not a consistent finding
Temperature usually normal or slightly elevated (99 5° to 100 F)
Blood pressure normal

Laboratory Data — Severe hemoconcentration and low levels of blood sodium chloride are the outstanding laboratory findings in heat cramps An increase in total serum protein to 9 per cent and of red blood cells to 5 5 million is found in the average case[43] A moderate leucocytosis usually exists occasionally rising to 18 000 The serum chloride and serum sodium levels are very significantly diminished chloride av 95 m eq sodium av 130 m eq The blood non protein nitrogen is elevated to 50 or 60 mgm per 100 c c The blood sugar occasionally may be low[56] but usually it is normal[48] In either case glucose administered intravenously does not effect the cramps Serum calcium and potassium are elevated

The urinary sodium chloride is extremely low. The urine may be entirely free of chloride and normal amounts may not reappear in the urine for several days even though salt is being administered. The body may retain as much as 30 to 50 grams of sodium chloride during this period. Albumin and casts are frequent but disappear as soon as hydration is reestablished.

Treatment. — One's first reaction upon observing a case of severe heat cramps is to administer morphine for relief of pain. But neither the spasm nor the pain is relieved by morphine[61, 63, 65]. Furthermore it is advisable that narcotics and sedatives not be used in the various forms of heat disease because of their undesirable effects upon the heat regulating mechanisms of the body (see Treatment of Heat Stroke).

The administration of salt and water, however, results in rapid relief of the entire syndrome. The treatment of heat cramps therefore is precisely the same as that outlined for heat exhaustion (see Treatment of Heat Exhaustion). Within a few hours the patient has recovered completely and usually is able to go back to his job on the same day or the following one. No untoward sequelae are recognized.

Prevention. — Heat cramps can be prevented by insuring adequate replacement of salt and water as they are lost during periods of excessive sweating. The remarks made under the heading Prevention of Heat Exhaustion are applicable in all respects to the prevention of heat cramps.

Thermogenic Anhidrosis
(Failure of the Sweating Mechanism)

This is alleged to be a newly recognized syndrome which the authors[9] believe to be distinct from the three classical varieties of heat disease. It was observed to occur in soldiers who were training in the American desert area, where the humidity is low and where mid-day temperatures approach 120° F.

The major characteristics of the syndrome are as follows:

1. It occurs during direct exposure to sunlight in the hottest part of the day. The individual may or may not be working.
2. It is frequently preceded for several days or weeks by unusually intense sweating.
3. Shortly before the onset of symptoms, sweating ceases below the level of the neck but profuse sweating of the head and neck continues.
4. The patient then complains of subjective warmth, weakness, dizziness, headache and shakiness. Transient periods of unconsciousness may occur.
5. On examination the skin is warm and dry from the neck down and a papulosquamous eruption is observed over the dry area.
6. Rectal temperature ranges from 99° to 10 ° F.
7. A few determinations showed normal blood chloride levels.
8. Blood pressure was not reported.

9. Rest and cool environment results in restoration of sweating function and complete normality in 9 to 24 hours. Administration of salt is said not to effect the symptoms.
10. It is suggested that the mechanism of this disturbance may be temporary functional paralysis of the thermoregulatory center resulting from the initial period of hyperhidrosis.

Comment. — The idea that initial excessive sweating might, by fatiguing the sweat glands or by some other mechanism, be the cause of sweat stoppage is not new[71], but it has not yet been proven. Although cessation of sweating is an outstanding characteristic of heat stroke, it is not infrequently observed in cases of heat exhaustion or heat cramps. Continuation of sweating of the face and neck, suggest an unusual syndrome, but we[7] have observed transient periods of the same phenomenon in men subjected to work in humid heat and not exposed to sunlight. These men have shown mild increases in rectal temperature above their usual levels during the period of sweat stoppage and have complained of fatigue and warmth. Within a day or two normal sweating began again despite continuation of work in the heat.

It is our belief that the syndrome described by Wolkin and associates [0] represents a combination of mild heat exhaustion and mild heat retention, the latter condition frequently being associated with functional instability of thermoregulatory center. Under these conditions it is to be expected that the administration of salt, even though correcting an element of salt deficiency, would not relieve the symptoms arising from heat retention, lack of sweating. Rest and a cool environment is effective.

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CHAPTER XIX B

SUNBURN

By CYRUS C STURGIS

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The action of the sun s rays in producing the changes in the skin known as sunburn is familiar to almost all from personal experiences It is not generally appreciated however that a prolonged exposure may be followed by striking changes in the skin which are associated with severe constitutional symptoms Within recent years an increasing interest has been awakened in the biological action of light due to the more widespread use of heliotherapy and the reaction of the skin to exposures of the Roentgen ray and radium

The Action of Sunlight on the Skin

The visible light rays are not as a rule active in producing changes in the skin as they are not absorbed The epidermis most readily absorbs the ultra violet rays and this results in the characteristic changes known as sunburn According to Hill[1] an examination of the skin five days after an erythema produced by light shows serous swelling and many mitoses in the deeper layer of epidermic cells There may be a marked increase in the diameter of the small skin vessels and a stagnation of blood which is followed by a visible edema and active diapedesis from the vessels Blisters form when sufficient serum collects between the horny and granular layers of the epidermis Light rays not only produce injury by direct action on the cells of the skin but also by the indirect action on the endothelial cells of the skin vessels which is followed by edema and thrombosis The reaction is followed eventually by pigmentation which results from the deposition of the pigment melanin in the basal cells of the epidermis as Clarke has emphasized According to this observer melanin is assumed to be the end product of the oxidation of tyrosin or a related compound and this reaction is probably produced through the action of an oxidizing ferment which has been termed tyrosinase While one function

of the pigment is to afford protection against an excessive radiation, it also results in a maximum absorption of radiant energy in the basal cells of the epidermis and may, therefore, cause an increased light reaction at this point, as Clarke has stated

SYMPTOMS AND SIGNS

Severe sunburn in adults occurs most frequently following an unduly prolonged initial exposure during the early part of the summer at the beginning of the open air bathing season The condition may be produced in infants or young children as a result of carelessly leaving them in the direct sun s rays for a relatively short time The action of the sun is most intense around noon day during warm weather and in the absence of wind In the presence of the latter factor there is more of a tendency to pigmentation with a less striking hyperemic reaction There is a marked variation in the susceptibility of different persons to solar rays, for it is well known that blonde individuals may suffer more serious injury than those with a dark complexion Negro races are afforded protection on account of their natural pigmentation

Following a short exposure to the sun there may appear in the course of a few hours a mild erythema of the skin which produces no discomfort or other symptoms than a feeling of warmth which persists for twelve to twenty four hours Serious symptoms may result however from a more prolonged exposure of a wide area of the skin These do not manifest themselves at the time the damage is accomplished and usually the individual is unaware of the symptoms which are soon to follow The initial symptoms appear in one to two hours and consist of a not unpleasant feeling of warmth which gradually changes to an intense burning localized to the injured areas At this time the skin shows a striking diffuse erythema and marked tenderness develops Within a few hours following the earliest symptoms a chill may be experienced which is followed by a temperature rise to 101° F or higher At this time the skin is an angry red and radiates heat which is apparent to the hand when held several inches from the involved area The combination of an erythematous, tender skin and fever makes sleep and rest difficult to obtain As the exposed areas are frequently those which are not covered by a bathing suit it is almost impossible for a person so affected to lie in a position without exerting pressure on one of the tender areas

Within twelve to eighteen hours after the earliest symptoms the skin may show evidence of pitting edema which is most extensive about the dependent parts as the ankles if this region has been exposed In addition to other changes the skin becomes so exquisitely tender that even the pressure of light clothing is unbearable Further discomfort arises, if the skin over the legs has been involved as a very painful throbbing becomes apparent when the position i changed from lying to a sitting or standing posture Blisters may appear in a

variable period of time depending on the extent of the injury and the suscep tibility of the individual They may be extensive but are usually superficial as shown by their covering which is frequently the thinnest layer of epidermis

The fever and cutaneous symptoms usually persist without abatement for forty-eight to seventy two hours and as a result of the distressing symptoms and lack of sleep irritability and some degree of prostration may occur The pain on attempting to walk may be so severe as to cause syncope As the constitu tional and local symptoms gradually subside the individual may again resume a normal life although tenderness over the involved areas commonly persists for a week or ten days Following this acute desquamation of the skin occurs usually in the form of peeling in large plaques which may be as large as the palm of the hand This frequently continues for as long as a week or more Pigmentation of the skin then appears which is probably a protective phenomenon against further effects of the sun s rays

Various other serious symptoms have been described such as delirium col lapse hematuria and other signs which may follow any severe cutaneous burn Transient albuminuria has been quite commonly encountered

Treatment

All individuals and especially those known to be susceptible should use cau tion in exposing themselves to the sun particularly on clear and warm days It should also be remembered that no immediate symptoms may be present to give warning of the severe skin involvement which follows later All initial exposure to the sun rays should be of short duration until a protective pigmen tation develops When this occurs it is possible to remain exposed for long inter vals without injury as evidenced by the apparent immunity of life guards on bath ing beaches and patients who have been systematically treated by heliotherapy Some protection is afforded by the application of an oily substance as olive oil to the skin which serves in part to absorb and reflect injurious rays

Mild sunburn requires no further treatment than the frequent local applica tion of a soothing lotion such as the following

Zinci Oxidi	15 0
Phenolis Liq	2 0
Liq Calc Hydrox ad	250 0

Ointments are objectionable as they cause the clothing or bed clothes to adhere to the skin In an extensive injury the most satisfactory method of treatment is to have the patient remove all clothing which comes in contact with the affected parts and remain in a room in which the temperature is maintained at a comfortable level A very soothing treatment for the skin is to use zinc stearate powder in abundance Much can be accomplished for the comfort of the patient

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CHAPTER XIX–B1

THE EFFECT OF COLD

By JOHN H. TALBOTT

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INTRODUCTION

The interest shown in the several features of the effect of cold upon the human body has been great during the past decade There are at least three major influences and several minor ones that have prompted this response

if a number of large, soft pillows are arranged in such a manner as to remove pressure from the painful skin areas Rest and sleep should be obtained for the patient by the use of codein if necessary and if the condition is serious enough, morphine sulphate 0 010 gm (1/6 gr) should be given In some instances, the most comfortable position for sleeping is obtained by the patient lying face downward, with pressure removed from the shoulders, if they are involved, by placing several large pillows under the thorax and abdomen Other patients find that sitting in a chair, well padded with pillows, and with the lower extremities elevated, gives the greatest opportunities for sleep

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cold which preceded many of the interests enumerated above and which has been pursued from time to time by clinical investigators and physiologists as is their custom in the pursuit of knowledge in many of the branches of physiology. Each of these subjects will be treated in the following discussion although the order will be altered considerably and other phases of the effect of cold not enumerated already will be included.

Range of Physiological Temperature

Man is a homoiothermic creature and is endowed with the property of maintenance of internal body temperature within a very small range[14,15,16]. This range has been found to be somewhat greater however than that stated formerly in standard reference books. A temperature fluctuation as great as 1.5 C (7 F) may be observed in persons enjoying good health. It has been noted that some persons have a rectal temperature above 37 C (99 F); a minimum of 36.1 C (97 F) has been recorded in others in the the absence of any recognized disease. Strenuous muscular exercise may raise the temperature 1.5 to 2.5 C (2.7-4.5 F) in the course of a few minutes in a healthy athletic individual, a fact not appreciated generally. Hence caution should be exercised in interpreting the temperature of an adult immediately following physical activity or that of a child after a strenuous bout of playing. On the other hand the rectal temperature in a child may decline 0.5 C (0.9 F) during an afternoon nap[4].

The skin or surface temperature of the body is several degrees below the temperature of internal organs and is related directly to that of the environment immediately adjacent to the skin. If the body is clothed adequately and the environmental temperature is approximately 5 C (75 F) the skin temperature of the back and chest may be only a few degrees below the rectal temperature. Under similar circumstances the skin of the uncovered hands may approach environmental temperature, while the surface temperature of the arms and the legs is between finger and back temperatures. As the environmental temperature falls and warmer clothing is added the reaction of the body is to maintain the internal temperature level. Nevertheless a person at rest in a sub zero environment and thought to be adequately clothed according to American concepts experiences a sensation of general bodily chilliness before an hour has elapsed. Within this time and prior to the onset of gross shivering the skin temperature of the back will be only a few degrees

1 The researches of Fay and Smith in Philadelphia[1,2] in the treatment of carcinoma by the general lowering of body temperature as well as by the local application of cold appeared to expose new and significant possibilities in the control of malignant tissue. Essentially all of the beneficial effects which they anticipated initially, have failed to be confirmed; nevertheless, a portion of the existing knowledge of the physiology of cold and the therapeutic value of low temperatures may be traced to their studies.

2 A logical extension of the findings of the Philadelphia investigators was the use of cold in the surgical handling of crushed or gangrenous extremities as advocated by Allen.[3] Cold exerts an anesthetic action directly upon tissue cells and reduces metabolism significantly. The protoplasmic activities are inhibited sufficiently so that the survival time of devitalized tissue is prolonged in spite of a reduced oxygen supply. Extremities may be immersed in ice water for several days without thrombi forming in the blood vessels or the development of other serious sequelae. Furthermore primary and secondary shock may be prevented by the local application of cold.

3 The recent war has prompted the systematic study of the protection of man against environmental extremes. The conflict was global in scope and demanded that large numbers of fighting men be exposed to extenuating climatic conditions. Service in the far north imposed a serious handicap upon protection of the foot soldier against dry cold. Modification of clothing and sleeping gear was imperative in order to insure survival in sub zero temperatures.[4] The wet cold of battle areas in temperate climates lead to trench foot, a serious military problem which produced as many as 50 per cent of the total battle casualties in several major operations.[6] Members of the Air Corps on flight duty were subjected to extremely low but dry air temperatures. Meanwhile they were compelled to remain in an essentially immobile position and could not protect adequately peripheral portions of the body.[8] Finally immersion foot[9,10] was a military hazard for members of each of the services who were abandoned on a life raft from a ship at sea, or who were forced to bail out from an airplane over water.

Minor interests in the effect of cold include the following: 4 The "cold pressor" test[11] for the evaluation of vasomotor responses in patients with hypertension or other maladies. 5 The "cold assay" test for evaluation of adrenal cortical hormones.[12] 6 Hypersensitiveness to cold as an allergic or related response.[13] 7 The effect of exposure to cold upon alteration of resistance to infection. 8 The physiology of exposure to

though vasoconstriction is maximal[19] When the air temperature is below 5 C (77 F) it is only a matter of a short time before a nude male begins to shiver in order to counteract the heat loss The evidence is still insufficient whether or not there is an effective increase in metabolism prior to the onset of shivering Hardy and DuBois[20] have shown that females are endowed with a physiological advantage in a temperate environment A reduced heat production occurs in this sex at an air temperature of 30 C (86 F) owing to a thicker layer of subcutaneous fat The sweat loss in a lower temperature range is 10 per cent less than that of males and the temperature of the skin is about 1 0 C (1 8 F) cooler The comfort zone in which heat loss and heat production are in equilibrium extends over a range of 6 C (11 F) for females and over a range of not more than or 3 C (3 6 5 4°F) for males Thus females may be comfortable in cool air although lightly clad while males need more covering

Horvath and associates have studied the oxygen consumption of heavily clothed men sitting at rest in temperatures as low as 40 C (40 F) Metabolic increases of 13 53 and 74 per cent were recorded for the first second and third hours respectively Although shivering was present in most subjects during the third hour the rise in heat output during the first hour was not attributed by the investigators to this mechanism An increase in muscle tone to explain a rise in metabolic rate was considered as a possible explanation Exposure of nude subjects to air temperatures between 1 and 5 C (33 and 41 F) may be accompanied by violent enough shivering to lead to a 4 fold increase in oxygen consumption for hours and at slightly higher exposure temperature 8 C (46 F) a 3-fold increase for 4 hours Hemingway and Hathaway measured the action potentials of muscles in dogs by means of electrodes placed in the skin During exposure to cold the animals showed a 7 per cent rise in metabolism prior to shivering Burton and Bronk recorded the frequency of impulses of single muscle fibers and found no rise in metabolism until there was an increase in the number of impulses These studies suggest that an increase in metabolism is accompanied by an increase in muscle tone A similar increase in occult and involuntary muscle activity as recorded by the electromyograph in the absence of obvious shivering was noted by the author in unpublished researches on a series of patients during experimental hypothermia These observations are in keeping with the clinical findings that cold intensifies the knee jerk in man and that an increase in

below the rectal temperature. Meanwhile the surface temperature of the fingers and toes decreases progressively to the 7-13°C (45-55°F) range, and numbness or painful sensations appear in these members. Skin or surface temperatures of 0°C (32°F) have been recorded in a few persons before unbearable painful sensations have developed[1]. Continued exposure is followed by some decrease in rectal temperature, usually not more than 1.0°C (1.8°F). If physical exercise or application of external heat is not possible, under such circumstances undesirable sequelae set in. These may be delayed but not for long, by shivering, an ineffective form of physical activity. Serious reduction of body temperature and frostbite of the covered extremities and inadequately protected face are inevitable unless restorative measures are instituted.

The Regulation of Body Temperature

The regulation of body temperature in cool or cold environments is accomplished by nervous, chemical and physical agents, although the precise role that each plays is not defined clearly. Selected interruption of impulses of the central nervous system or localized destruction of nervous tissue in animals reveals that more than one area of the brain is associated with heat regulation. The hypothalamus is presumed to embody one area for protection against heat loss and another for prevention of heat gain. Destruction of either center results in failure of physiological processes following environmental exposure. Marked lowering of the body temperature may be produced upon exposure to minimal variations of air temperatures. On the other hand, the body temperature may be changed by the local application of heat or cold to the heat regulating center, but the stimulus required is greater than that encountered physiologically. Ranson and colleagues[13] have conducted extensive investigations upon the centers of the hypothalamus that exert an influence upon heat regulation through sympathetic impulses to the periphery. They have shown that removal of the sympathetic chain renders an animal more susceptible to the effects of cold. It is obviously difficult in man to demonstrate the action of these central nervous factors in heat regulation.

A balance between heat production and heat loss for a nude male at rest is achieved usually when the air temperature is between [illegible]8°C (8[illegible]°F) and 30°C (86°F). A slow fall in body temperature has been shown to be inevitable at an exposure temperature below [illegible]8°C even

5 fold The degree of cutaneous vasoconstriction is greater in the extremities than in the trunk and is greatest in the peripheral portions of the extremities[3] It is of interest that there are no vasoconstrictor reflexes demonstrable in the blood vessels of the forehead[6] In addition to vasoconstriction blood volume is reduced as another participating factor in the compensating mechanism[37] The concentration of hemoglobin in the blood increases as much as 20 per cent and urine output increases from 200 to 500 cc per hour in subjects who are in the horizontal position in cold environments Adolph and Molnar interpret the diuresis as a loss of fluid from the blood during decrease in blood volume If the subject is sitting however fluid leaves the blood stream and enters the extravascular spaces Shivering inhibition of active perspiration assumption of a compact body mass with flexion of the arms legs and thighs and active muscular movement complete the natural defenses of the body If these are ineffective protection against cold clothes must be added or artificial heat supplied

Protective Clothing

Cold weather clothing has been an integral part of human existence in certain areas of the world since history has been recorded Modern civilization however has shown relatively little scientific interest in this problem until the past decade and most of our precise knowledge is no older Inhabitants of the Far North rely heavily upon fur for protection In frigid regions of Europe and Asia either fur or quilted garments are used Western culture on the other hand is intimately familiar with neither fur nor quilted fabrics as basic protective materials in the composition of an ensemble Hence when the task of providing protective clothing for a large military force operating in frigid weather was under discussion it was readily apparent that much basic information need be sought The impetus for the evaluation of cold weather clothing emanated from certain projects initiated by the Military Planning Division of the Quartermaster Corps of the United States Army which were endorsed by the several subcommittees of the National Research Council

Unit of Measure—It was necessary first to devise a unit of measure for the definition of thermal insulation of clothing Gagge Burton and Bazett[38] have shown that the fundamental equation for thermal insulation may be expressed as

heat production is inhibited in animals exposed to cold after the muscles have been paralyzed by curare[6]

An increase in heat production as a result of hyperfunction of the thyroid as well as the adrenal glands has been assumed from certain studies of animals It has been recognized for some time that the thyroid of domestic animals is larger in winter than in summer Furthermore it has been shown experimentally that the thyroid of laboratory animals hypertrophies following exposure to cold[7] Ring[8], on the other hand concluded that the increased elaboration of thyroid hormone is not sufficient to account for the augmented heat production in animals He believes that increased adrenalin production motivated by the thyroid hormone is partially responsible Other evidence suggests adrenal cortical participation in the general reaction to cold Adrenalectomy in animals is followed by a lowered resistance to cold Since removal of one adrenal from a cat leads to increased shivering this phenomenon is thought to be a compensatory mechanism for loss of adrenal hormones from the operated side[9] Horvath[30] noted that cold provoked a smaller rise in heat production in uni-adrenalectomized animals than in normal controls Lawrence[31] showed that exposure to cold is followed by a rise in concentration of blood sugar in rabbits This was attributed to increased adrenal secretion A master control over thyroid and adrenals by the pituitary has been postulated by Wolf and Creep[3] Cold was not found to stimulate thyroid activity in hypophysectomized rats Although much remains to be defined in this field available evidence suggests that hormonal or chemical regulation of heat production plays but a small part in the physiological response to cold Nervous impulses through physical mediation and subsequent decrease of heat loss make the greatest contribution

Vasoconstriction is a potent mechanism for inhibiting heat loss by means of a decrease in the thermal conductance of peripheral tissues Although vasoconstriction is an efficient instrument, it exerts a maximal effect at a relatively high environmental temperature[33] Hardy and DuBois[19] found that heat loss was minimal at an environmental temperature of 28-30 C (82-86 F) Heat loss due to vasodilatation was increased at lower temperatures and at higher temperatures Spealman[34] also observed a point of minimum heat loss as judged by blood flow measurements in the hand at exposure temperatures varying from 5 to 35 C (41 to 95 F) Blood flow was minimal (0 9 cc /100 cc/min) in hands immersed in water at 15 C (59°F) If the temperature were colder (5 C) or warmer (35 C) the blood flow increased as much as

Where I_1 = insulation of clothing in *clo* units
T = temperature on the inner surface of thermal pathway (skin temperature)
T = temperature on outer surface of thermal pathway (air temperature)
H_1 = heat loss through the clothing in calories per square meter per hour
I = insulation value of air in *clo* units
3 09 = conversion factor

H_1 heat loss through the clothing in the case of a human subject is equal to the heat produced by the subject (H) plus the stored heat lost from the body (H) minus the sum of the heat lost in evaporating water from the lungs and skin surface (H) and in warming the inspired air (H_a)

This may be expressed as follows

$H_1 = H_m + H - (H + H)$

Where H_1 = heat loss through the clothing
H_m = metabolic heat produced
H = stored heat lost from the body (heat debt)
H = evaporative heat lost
H = heat lost in warming inspired air

Each of these quantities may be determined and expressed in calories per square meter per hour

It is apparent that in order to determine the insulation value in *clo* units of an item of clothing for a human subject the following data must be available

I = insulation value of air in *clo* units
T = average skin temperature
T = air temperature
H = metabolic heat produced
H = loss (or gain) in stored body heat
H = heat lost in evaporating water from the lungs and skin surface
H = heat lost in warming the inspired air

The several values are derived as follows

I the insulation value of the air in *clo* units in a constant temperature room is approximately 0 5 *clo*

T the air temperature

$$I = \frac{T_1 - T_o}{H}$$

Where I = Thermal insulation
T_1 = Temperature on one surface of the thermal pathway
T = Temperature on one surface of the thermal pathway
H = Heat flow across the pathway

In applying this equation to clothing[39, 40] it is necessary to consider I as being made up of the insulation value of the clothing plus the insulation value of air The equation then becomes

$$I_1 + I_a = \frac{T_1 - T}{H}$$

Where I_1 = insulation value of clothing
I_a = insulation value of air

Since the thermal insulation of air at various wind velocities and altitudes is known it is possible to subtract this value from the total insulation in order to determine the thermal insulation of the clothing

Considerable confusion arose in the past because of the number of units for the expression of thermal insulation In order to clarify this situation, Gagge and associates[38] introduced the *clo* (clo-thing) unit as a practical means of expressing thermal insulation of clothing The unit is defined as the insulation required to maintain in comfort a sitting and resting subject at 70 F, air movement 10 feet per minute and humidity not greater than 50 per cent It is approximately equal to the insulation provided by a wool street suit for a man By definition one *clo* has a value of 0 18 C per calorie per square meter per hour It is possible to express thermal insulation in *clo* units by means of the appropriate conversion factor regardless of the units of measure employed in determining temperature and heat flow

When heat flow is expressed in calories per square meter per hour and temperature in F the insulation value of clothing may be represented as follows

$$I_1 = \frac{3\ 09\ (T - T_a)}{H_{cl}} - I$$

Where I_t = insulation of clothing in *clo* units
T = temperature on the inner surface of thermal pathway (skin temperature)
T = temperature on outer surface of thermal pathway (air temperature)
H_t = heat loss through the clothing in calories per square meter per hour
I = insulation value of air in *clo* units
3 09 = conversion factor

H_t heat loss through the clothing in the case of a human subject is equal to the heat produced by the subject (H_m) plus the stored heat lost from the body (H) minus the sum of the heat lost in evaporating water from the lungs and skin surface (H) and in warming the inspired air (H_a)

This may be expressed as follows

$H_t = H_m + H - (H + H_a)$

Where H_t = heat loss through the clothing
H_m = metabolic heat produced
H = stored heat lost from the body (heat debt)
H = evaporative heat lost
H = heat lost in warming inspired air

Each of these quantities may be determined and expressed in calories per square meter per hour

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H = heat lost in warming the inspired air

The several values are derived as follows

I the insulation value of the air in *clo* units in a constant temperature room is approximately 0 5 *clo*

T the air temperature

T_s, the average skin temperature, is obtained from a series of skin temperature measurements and the values weighted.

H_m, the metabolic heat produced by the individual, is measured by means of an open circuit respiratory apparatus. Pulmonary ventilation, respiratory quotient and oxygen consumption are measured simultaneously.

H, the stored heat lost (or occasionally, the heat gained), has been shown to be equal to

$$H = \frac{T_a \times .83 \times W}{1.8 \times S.A.}$$

Where T_a = average body temperature
0.83 = specific heat of body mass
W = weight (9 in Kg.)
S.A. = surface area (in sq. meter)
1.8 = conversion factor for F to C

T_a, has been shown to be equal to $0.70 \times T_r + 0.30 \times T$

Where T = rectal temperature
T_s = average skin temperature

H_e, heat lost by evaporation of water vapor, has been shown to be equal to

$$H = \frac{0.0207 \times \text{pul. ventilation (L./hr.)} + 6.3}{S.A.}$$

Where 0.0207 = calories lost per liter of ventilation
6.3 = heat lost by insensible perspiration

$$H = \frac{0.00031\ (91.5 - \text{inspired air temp.}) \times \text{ventilation}}{1.8 \times S.A.}$$

Where 0.003 = calories per liter of air per C
91.5 = temperature of expired air F
1.8 = conversion factor F to °C
S.A. = surface area

Description of Available Items.—As noted above, the protective value of a suit of clothes of a man is approximately 1 *clo*, which is equivalent to 0.25 inch of a good insulating medium. The number of *clo* that can

be added to the body meanwhile permitting physical activity is strictly limited Approximately 3 *clo* protection is the best that can be devised with the most appropriate fabrics available The warmest glove provides little more than 1 *clo* and the warmest mitten *clo* The best cold weather footgear is similar in protective value to the mitten The most effective Arctic clothes devised by the Quartermaster Corps (3 *clo*) will provide protection for a man standing for unlimited time at a temperature not colder than −9 C (+15 F) If the weather is colder he must keep active or seek shelter At − 6 C (−15 F) a man in Arctic clothing becomes unbearably cold after standing 3 hours

Protective value of clothing is dependent in large part upon the effective air trapped within the interstices of the fabric rather than upon the amount of fabric within a given space It is commonly believed that if one pair of wool socks will provide certain protection when worn within a given pair of shoes two pair of socks will double or at least increase protection when worn within the same shoes This is a false assumption If one wool sock fits comfortably within a shoe a second sock will add little or nothing in insulation value because the volume of entrapped air about the foot is not increased If the second sock produces even a minimal amount of constriction to the circulation the foot may cool at a more rapid rate than with one sock only Extremities stay warmer when circulation is not reduced by constriction

In order to provide maximum protection against sub zero cold the entire body should be covered with the maximum number of layers of light weight material (wool) consistent with minimum constriction of the circulation of the skin so as to permit adequate movement of extremities and trunk Outside of these layers of wool containing entrapped air there should be a light weight wind breaker (cotton) over all parts of the body except feet and palms of hands Leather should be the outer cover for soles of shoes and either leather or a durable cotton fabric for palms of mittens

A final factor in regard to cold weather clothing concerns disposition of moisture from the skin and lungs The body loses moisture during exposure to the cold as well as during exposure to the heat Insensible loss is a continuous process Sensible loss on the other hand is intermittent but usually is of greater magnitude when heavy clothing is worn than is assumed ordinarily Moisture is driven from the skin into the protective materials surrounding the body because of the temperature gradient As moisture accumulates between or within the fibers in fabrics heat loss is augmented and insulation efficiency is diminished

Ts, the average skin temperature, is obtained from a series of skin temperature measurements and the values weighted

H_m, the metabolic heat produced by the individual, is measured by means of an open circuit respiratory apparatus Pulmonary ventilation respiratory quotient and oxygen consumption are measured simultaneously

H the stored heat lost (or occasionally, the heat gained), has been shown to be equal to

$$H = \frac{T_a \times 83 \times W}{1\ 8 \times S\ A}$$

Where T_a = average body temperature
0 83 = specific heat of body mass
W = weight (9 in kg)
S A = surface area (in sq meter)
1 8 = conversion factor for °F to °C

T , has been shown to be equal to 0 70 × T_r + 0 30 × T ,
Where T_r = rectal temperature
T = average skin temperature

H_e heat lost by evaporation of water vapor has been shown to be equal to

$$H = \frac{0\ 0.07 \times \text{pul ventilation (L /hr)} + 6\ 3}{S\ A}$$

Where 0 0.07 = calories lost per liter of ventilation
6 3 = heat lost by insensible perspiration

$$H_a = \frac{0\ 00031\ (91\ 5 - \text{inspired air temp }) \times \text{ventilation}}{1\ 8 \times S\ A}$$

Where 0 003 = calories per liter of air per C
91 5 = temperature of expired air F
1 8 = conversion factor F to C
S A = surface area

Description of Available Items —As noted above, the protective value of a suit of clothes of a man is approximately 1 *clo*, which is equivalent to 0 .5 inch of a good insulating medium The number of *clo* that can

be added to the body, meanwhile permitting physical activity, is strictly limited. Approximately 3 *clo* protection is the best that can be devised with the most appropriate fabrics available. The warmest glove provides little more than 1 *clo* and the warmest mitten 2 *clo*. The best cold weather footgear is similar in protective value to the mitten. The most effective Arctic clothes devised by the Quartermaster Corps (3 *clo*) will provide protection for a man standing for unlimited time at a temperature not colder than −9° C (+15° F). If the weather is colder, he must keep active or seek shelter. At −26° C (−15° F) a man in Arctic clothing becomes unbearably cold after standing 3 hours.

Protective value of clothing is dependent in large part upon the effective air trapped within the interstices of the fabric rather than upon the amount of fabric within a given space. It is commonly believed that if one pair of wool socks will provide certain protection when worn within a given pair of shoes, two pair of socks will double or at least increase protection when worn within the same shoes. This is a false assumption. If one wool sock fits comfortably within a shoe, a second sock will add little or nothing in insulation value because the volume of entrapped air about the foot is not increased. If the second sock produces even a minimal amount of constriction to the circulation, the foot may cool at a more rapid rate than with one sock only. Extremities stay warmer when circulation is not reduced by constriction.

In order to provide maximum protection against sub-zero cold, the entire body should be covered with the maximum number of layers of light weight material (wool) consistent with minimum constriction of the circulation of the skin so as to permit adequate movement of extremities and trunk. Outside of these layers of wool containing entrapped air there should be a light weight wind breaker (cotton) over all parts of the body except feet and palms of hands. Leather should be the outer cover for soles of shoes and either leather or a durable cotton fabric for palms of mittens.

A final factor in regard to cold weather clothing concerns disposition of moisture from the skin and lungs. The body loses moisture during exposure to the cold as well as during exposure to the heat. Insensible loss is a continuous process. Sensible loss, on the other hand, is intermittent but usually is of greater magnitude when heavy clothing is worn than is assumed ordinarily. Moisture is driven from the skin into the protective materials surrounding the body because of the temperature gradient. As moisture accumulates between or within the fibers in fabrics, heat loss is augmented and insulation efficiency is diminished.

Hence, clothing always should be as dry as possible for maximum protection and impermeable barriers (rubber or rubber substitutes) should be avoided whenever possible If rubber footgear is worn over wool socks there is no ready channel for escape of moisture, it accumulates in socks, and insulation value diminishes A rubberized raincoat produces a similar result when worn over the torso

Physiological Effects

Sensations of Cold and Pain—The temperature of the skin probably is the principal factor in the subjective feeling of coolness or warmth When skin temperature is approximately 33° C (91 F) the person feels comfortable, neither cold nor warm The subjective feeling of coolness and the temperature of the skin depend in part upon vasomotor constriction or dilation If vasoconstriction is inhibited, in spite of a fall in body temperatures the subject feels comfortable If a person after exposure to a cold bath is removed to one of slightly higher temperature, several of the protective reflexes are less effective and the fall in body temperature experienced while at the warmer temperature is greater than would have occurred had conditioning by the first and slightly colder bath been omitted The sensation of cold may be caused by a change of skin temperature of not more than 0 004° C per second The precise value of skin temperature is less effective as a stimulus The skin may be conditioned to cold following a very short exposure as is suggested by the familiar experience of placing the right and left hand each in a water bath of different temperatures After a minute or so, if both hands are placed in a bath with a temperature between the two extremes the hand that was in the warm bath feels cool and the hand that was in the cool bath feels warm

The application of cold to the skin of a person in equilibrium with room temperature is associated with a cold feeling and is followed by a sensation of pain if the cold is of sufficient intensity When an area of the body as large as the hand is immersed in cold water there may be an elevation of the blood pressure as well a phenomenon which has been designated as the cold pressor test[11] Wolf and Hardy[11] have shown that regardless of the strength of the stimulus maximum pain is reached within 60 seconds and may be observed at bath temperatures as warm as 18 C (64° F) The sensation of pain is independent of the sensation of cold and as the stimulus persists pain gradually subsides

and is replaced by a sensation of "pins and needles", which soon in turn ceases. Although the extremities have received the greatest attention in studies concerning this aspect of the effect of cold, pain may be induced on most parts of the body. The stimulus required for the production of pain is related to the thermal gradient in the exposed tissues and is mediated through small, non myelinated fibers of class C.[11] Subsidence of pain after the first minute following exposure is associated with a decrease in the temperature gradient as the tissues approach the temperature of the cold stimulus. Furthermore, if local cooling proceeds at a sufficiently slow rate the exposure temperature may be lowered to 0° C (32° F) without the development of pain. Sympathectomy augments the intensity of pain. The depth that cold may penetrate and the temperature of the underlying tissues have been investigated by Bierman and Friedlander.[12] Application of an ice bag to the calf of a male subject is followed within 2 hours by a drop in muscle temperature of more than 8° C (15° F) as measured by thermocouples placed in the muscle.

Plethysmographic studies reveal a decrease in amplitude of pulsation of the digital artery which parallels inversely the intensity of the cold pain experienced. Elevation of the blood pressure is thought to be an index of the general reaction of the subject to cold pain and may be inhibited significantly by previous ingestion of a barbiturate. The arteriolar constriction, on the other hand, has been shown to be a local response to cold. Following arteriolar constriction the capillaries dilate as a compensatory response.[13] Lewis postulated the liberation of a histamine-like substance as a cause of the dilatation due to excitation of the axone reflex.[14] Continued immersion of a hand in iced water at +5° C (41° F) produces swelling and redness. Increase in volume occurs in both skin and subcutaneous tissues and may amount to as much as 15 per cent of the original volume. Analysis of the protein content of the edema fluid showed it to be high, a finding interpreted by Lewis as evidence of an inflammatory process.[4]

If a nude person is exposed to an environmental temperature below 22° C (72° F) the subject becomes chilly after a short time.[15] The surface layers of the body cool rapidly and heat elimination exceeds heat production. Radiation accounts for approximately 70 per cent of total loss at 22° C; this percentage decreases rapidly as the external temperature is elevated. Vaporization dissipates only a small percentage of total heat at 22° C but almost 100 per cent at 35° C (95° F). These changes are associated with a minimal alteration in basal oxygen consumption. The cooling of the clothed body at 18° C (65° F) is a more gradual

Hence clothing always should be as dry as possible for maximum protection and impermeable barriers (rubber or rubber substitutes) should be avoided whenever possible. If rubber footgear is worn over wool socks, there is no ready channel for escape of moisture, it accumulates in socks and insulation value diminishes. A rubberized raincoat produces a similar result when worn over the torso.

Physiological Effects

Sensations of Cold and Pain.—The temperature of the skin probably is the principal factor in the subjective feeling of coolness or warmth. When skin temperature is approximately 33° C. (91° F.), the person feels comfortable, neither cold nor warm. The subjective feeling of coolness and the temperature of the skin depend in part upon vasomotor constriction or dilation. If vasoconstriction is inhibited, in spite of a fall in body temperatures the subject feels comfortable. If a person after exposure to a cold bath is removed to one of slightly higher temperature, several of the protective reflexes are less effective, and the fall in body temperature experienced while at the warmer temperature is greater than would have occurred had conditioning by the first and slightly colder bath been omitted. The sensation of cold may be caused by a change of skin temperature of not more than 0.004° C. per second. The precise value *of skin temperature is less effective as a stimulus.* The skin may be conditioned to cold following a very short exposure as is suggested by the familiar experience of placing the right and left hand each in a water bath of different temperatures. After a minute or so, if both hands are placed in a bath with a temperature between the two extremes the hand that was in the warm bath feels cool and the hand that was in the cool bath feels warm.

The application of cold to the skin of a person in equilibrium with room temperature is associated with a cold feeling and is followed by a sensation of pain, if the cold is of sufficient intensity. When an area of the body as large as the hand is immersed in cold water, there may be an elevation of the blood pressure as well, a phenomenon which has been designated as the "cold pressor test."[11] Wolf and Hardy[11] have shown that regardless of the strength of the stimulus maximum pain is reached within 60 seconds and may be observed at bath temperatures as warm as 18° C. (64° F.). The sensation of pain is independent of the sensation of cold, and as the stimulus persists, pain gradually subsides

Lewis ascribes these reactions to tissue injury related in part to release of histamine like substances

Local application of cold upon the motility of the gastrointestinal tract was studied by Bisgard and Nye[0] Motility was inhibited by the swallowing of ice water but was stimulated by the application of ice to the abdominal wall Abdominal application of ice increased gastric acidity and contents of free acid as well as of total hydrochloric acid Persons suffering from angina pectoris have reduced tolerance to cold air or to local application of cold Since angina pectoris is believed to be associated with constriction of the coronary vessels the vasoconstrictive effect of cold is assumed to be the mode of operation[1] Patients afflicted with bends have a longer period of distress in a cold environment than a warm one[2] In animals the toxicity of morphine paraldehyde sodium pentobarbital strychnine, nicotine amphetamine cocaine and procaine respectively is increased at low environmental temperatures[3,4]

Moritz and Weisiger[5] investigated the inhalation effect upon dogs of extremely cold blasts of air Dried air as cold as minus 100 C (148 F) for periods varying between 0 and 133 minutes was the stimulating agent At the time that the air reached the bifurcation of the trachea it was not colder than +18 C (64 F) Increased activity of the mucous secreting glands was a constant response There was local destruction of the superficial epithelium in some dogs In no instance was there evidence of injury to the lower portion of the trachea bronchi or alveolar tissues The rapid warming of the cold dry air with resultant minimal damage is related to the fact that dry air has an extremely low heat capacity The number of calories required to produce a great rise in the temperature of dry air may be provided by the heat derived from the cooling of a small amount of tissue by a few degrees only These experiments cast doubt upon the existence of a condition which has been called frozen lungs , a malady assumed to be caused by direct inhalation of air at extremely low temperatures Persons exposed to sub-zero air usually breathe through the nose, partially closed lips or through a face protection (scarf or mask) It can be assumed that such simple protective procedures are adequate to prevent any serious sequelae to the respiratory passages in conscious and alert persons

Endocrine Glands —A discussion of the effect upon the thyroid and adrenal glands following exposure to cold was introduced above, other aspects remain to be considered Hartman and associates[6] in 1931 noted that adrenocortical extracts exerted a beneficial effect upon adrenal

process Skin over the exposed parts such as ears and fingers cool at the most rapid rate and eventually approach the temperature of the surrounding air

Shivering—The mechanism of shivering and the production of a chill are pertinent to the discussion even although a chill is associated usually with an elevation of body temperature and not the reverse Since shivering following exposure of animals to cold occurs above but not below the level of transection of the spinal cord[16], the shivering center is presumed to be in the medulla or hypothalamus The rhythmicity and rate of shivering are determined peripherally by a mechanism which involves the proprioceptors and resembles that of a reflex clonus The rate in the normal animal is close to the resonant frequency of the moving part[17] The purpose of the chill in disease is obscure but the role in temperature regulation is important[18] A chill is associated with a marked increase in heat production and a rise in internal temperature Changes in heat elimination from vasoconstriction and drop in skin temperature may be slight or absent An increase in heat elimination has been observed in selected instances Other physiological changes include a decrease in heart rate, an irregular respiratory rate, a slight rise in blood pressure and a decrease in the white cell count

Vasoconstriction—General exposure of the clothed body is followed by constriction of the vessels of the skin as is local exposure Blood flow[19] is diminished which in turn leads to a diminution of heat loss Lewis[13] identifies 3 distinct reactions to vasoconstriction 1 Direct and persistent response of superficial vessels to cold 2 Immediate general but transient vasoconstriction by reflex action through the central nervous system This response is succeeded and replaced by the third 3 Cool venous blood returning from exposed areas lowers the temperature of the blood in the general circulation This acts also upon the central nervous system and produces general vasoconstriction As cooling continues the temperature of the limb falls At 10 C (50 F) or lower the skin is benumbed, fine touch sense is diminished, and the muscles of the limbs are less efficient

Local Reactions to Cold—Two reactions follow cooling of the skin below 0 C for short periods of time[17] Freezing may take place, if moisture is present on the surface, otherwise the skin may be supercooled to temperatures as low as -15 C (5 F) Wheals develop following either reaction Skin that has been frozen becomes red and tender for several days, which in time is followed by desquamation and pigmentation

temperatures as low as 34 C (93 F) in a patient with an unexplained clinical condition An attack of low temperature appeared annually for several years and was accompanied by sweating and chills Except for these isolated instances, hypothermia usually follows continuous exposure to a low environmental temperature under conditions such that heat production cannot be increased so as to compensate for heat loss

Artificial hypothermia in the clinic and exposure hypothermia out of doors are the conditions usually encountered The lower limit, to which body temperature may be reduced in humans without leading to a fatal result lies somewhere between 1 and 24 C (70 75 F) In 1875 Reincke[6] reported the findings from five inebriated persons who had been exposed accidentally to the cold The rectal temperatures after admission to the hospital of the two who recovered, were 4 and 30 C (75 86 F) respectively The three who did not recover had temperatures of 26, 27 and 8 C (79 5 80 6 83 1 F) respectively During therapeutic reduction of body temperature Fay[1] observed a minimum of 25 C (75 F) during life in one patient who did not recover In a series of patients observed by the writer[66] temperatures of 3 2 and 23 9 C (74 75 F) respectively were noted in two patients An uneventful recovery followed in each instance Critical levels of hypothermia have been reported for homoiothermic animals (non hibernating mammals) as follows the cat 16 C (61 F) the domestic rabbit o C (68 F), the monkey 14 C (57 F) the dog C (72 F) and *the rat 13 C (55 F), respectively*[67 68 69] *The heat regulating mechanism* is presumed to cease operating in animals below 4 C (75 F) and a continued fall in body temperature proceeds at the same rate as that in an inanimate body If the animal subsequently is warmed the thermal regulating mechanism begins to operate at approximately 4 C The body temperature may approach o C without causing death in the hibernating animal Lower forms of living material[9] which tolerate desiccation such as seeds bacteria and bacterial spores protozoan cysts and nematodes can approach the absolute zero without being killed The large majority of plants and animals however are killed at near freezing temperatures Some organism such as insect larvae can resist temperatures as cold as - o C and the freezing of a considerable portion of their total cellular fluid Others such as the mollusks the amphibia and the fishes are able to support the formation of some ice but they die when a significant portion of their body water solidifies

ectomized rats exposed to low temperatures Desoxycorticosterone acetate has a similar but less potent effect upon mice[7] The lowered resistance to cold of small animals that have been adrenalectomized has been used as a test for assay of cortical extracts[1, 8] Likewise, maintenance or restoration of body weight by the administration of thyroxin to rats simultaneously treated with the anti thyroid drug, thiouracil, has been used for the assay of the thyroid hormone The rate of thyroid enlargement in an environmental temperature of 1 C (34 F) was approximately double that observed in an environmental temperature of 25 C (77 F)[9] Additional evidence concerning the importance of the intact thyroid in protection against cold has been reported by Le Blond and Gross[60] Thyroidectomized rats were exposed to a temperature of 2 C (36 F) If exposure were instituted immediately following thyroidectomy, survival was approximately 1 week If exposure were delayed until stored thyroxine had been depleted, the average survival time was less than 2 days

Hypothermia—The general application of cold to anesthetized human beings or animals or to those, whose ability to escape from the cold environment has been inhibited, leads to a lowering of the body temperature This reaction has been described in medical reports in recent years as "freezing", 'frozen sleep", 'hibernation', "refrigeration' and 'crymotherapy" An objection may be raised against each of the terms Freezing and 'frozen sleep" are misnomers No part of the body is frozen in fact, during most of the treatment the body is exposed to temperatures above 0 C (32 F), and the purpose of the procedure is to lower body temperature, meanwhile exercising great care in order to avoid freezing any tissue Hibernation is not a correct biological designation for humans, refrigeration refers to the procedure applied rather than to the physiological results Crymotherapy is a modification of cryotherapy and connotes the definitive use of cold for treatment On the other hand hypothermia[61] refers to the specific reduction in body temperature and is the opposite of hyperthermia Although it too has certain disadvantages it is believed to be preferred to the other terms suggested

Hypothermia has been used also to describe a pathological lowering of the body temperature from causes other than exposure to cold Reimann[6] has described a syndrome associated with an unusually low rectal temperature He attributed the hypothermia to an undetermined infectious agent A fall in body temperature to a level as low as 35°C (96°F) may accompany insulin coma[63] Hoffman and Pibirs[64] reported

as 14 or 16 per minute in non hibernating animals exposed to cold. The changes in pulse and blood pressure are associated with a marked vasoconstriction venous as well as arterial. Obliteration of peripheral venous channels such as may be observed during casual exposure of an extremity to cold is first noticed. Drawing of venous blood becomes very difficult and may be impossible in a person who presents no such difficulty at a normal body temperature. Constriction of the large arteries occurs with continued hypothermia and frequently one is able to elicit neither the radial nor brachial pulse nor to obtain a blood pressure measurement in the customary clinical manner. Although the blood pressure and peripheral pulse may be unobtainable for several hours detectable vascular occlusion or thrombosis is not a complication. Obviously blood does flow in the vascular channels in the extremities as well as through the vital organs. There is a decrease in volume of circulating blood as measured by the dye method and a delay in movement of blood from arm to lung as measured by circulation time. The respiratory rate in dogs during hypothermia has been reported as low as 3 per minute.

Cardiac arrhythmia sinus arrhythmia and auricular fibrillation are observed frequently in hypothermia. The lower the body temperature the greater the likelihood of the development of an arrhythmia. Electrocardiograms show marked alterations[3]. These include in addition to the arrhythmia an alteration in the form of the final ventricular deflexion a prolongation of electrical systole a high take off of the T waves and a diphasic T. During recovery the QT interval does not return to normal at once in fact several days may elapse before this occurs. Tomaszewski[71] has reported detailed observations on a man aged fifty four who suffered from accidental exposure to the cold but did not die until after he had been observed in the hospital for several hours. The heart rate was 1 per minute when he was seen first. The rate increased to 44 before death. The electrocardiogram showed prolongation of the P R interval low voltage and delayed conduction time.

Pupillary reflexes disappear in human beings during hypothermia as they do in animals crossed tibial reflexes and absence of the plantar response have been observed also. The loss of nerve conduction appears to be a direct effect of profound cooling. It will be recalled that exposure to cold without hypothermia leads to hyperactivity of the reflexes. There is a complete restoration of the depressed nervous responses during recovery from hypothermia.

The induction of therapeutic hypothermia in man is accomplished by the parenteral administration of a quantity of a barbiturate or other sedative sufficient to produce narcosis for 45 to 60 minutes The patient then is placed nude in an environment of approximately 0°C Either especially constructed blankets or cracked ice may be used The body temperature begins to drop by the time that the anesthesia has begun to wear off and continues to drop at a rate of from 0 5-1 5 C per hour When the temperature is below 32 C (90°F), further anesthesia is unnecessary The temperature may be maintained within the range 27-32 C (80 90 F) for several days by alternating cold with a cool environment Patients have been maintained in a state of hypothermia for as long as 8 days[1] The subjects, usually, are drowsy and stuporous during hypothermia but they are not comatose, unless they are heavily sedated or unless the body temperature is below 27°C (80 F) Liquids containing minerals, vitamins and food stuffs may be administered from time to time by means of a stomach tube Gastric absorption appears to proceed at an adequate rate during hypothermia There have been few serious post-treatment complications The third patient in the authors series died[1] The mechanism of death in this case was interpreted as too rapid restoration of body temperature The few fatalities during or immediately following hypothermia have been attributed to cardiovascular failure or pneumonia It is of interest, however, that usually neither pneumonia nor upper respiratory disease is observed following marked depression of internal temperature When it is deemed desirable to terminate hypothermia induced therapeutically, which usually is an arbitrary decision the source of cold is removed and the external environmental temperature is allowed to approach 21 C (70 F) Gradual restoration of body temperature not more than 1 C per hour is believed to be a safer procedure than a more precipitous climb Some patients develop minimal edema of the extremities for a few days after hypothermia This is probably related to the phenomenon described by Lewis[41]

There are several significant physiological and biochemical changes that accompany hypothermia Alterations in the vascular system develop early and are profound in magnitude but in most instances are merely exaggerations of the physiological effect of cold Following an initial rise of pulse and blood pressure there is a gradual decline of each until the minimal body temperature is reached The heart sounds are muffled after induction and the heart rate is decreased but does not fall below 50 per minute if the rhythm is regular The heart rate may be as slow

anesthetized cat following cooling Intermittent and incoordinated twitching of single units appeared when the rectal temperature fell below 34 C (93 F) A rise of oxygen consumption followed shortly The response appeared first in the muscle of the head and thorax next in superficial muscles of the extremities and lastly in the deep muscle of the extremities The response of a given muscle increased in regularity by the number of active units and in frequency from 5 to 12 per second Coordinated groupings of discharges appeared later and resulted in gross tremors and shivering (11 per second) A single unit discharged only once in each group Pupillary reflexes disappear in human beings during hypothermia[80], and the normal plantar response is reversed Restoration of these responses is achieved by the time the temperature is normal

During the war there was ample opportunity to observe soldiers and sailors suffering from hypothermia following immersion Two excellent clinical reports on this subject have appeared Molnar[81] reviewed the records on file in the Bureau of Medicine and Surgery of the U S Navy of approximately 50 men who had been rescued at sea following a period of exposure It was apparent from his study that exposure to sea water at temperature of 16 C (60 F) or less for more than one hour was critical Immersion could be tolerated for many hours at sea water temperatures of 21 C (70 F) or above Spealman[8] noted a similar critical temperature (1 C) in experimental studies on humans Dogs usually responded in an analogous fashion Occasionally however they were able to maintain temperature equilibrium for as long as 5 hours at an immersion temperature of 0 C Adolph and Molnar compared exposure time and decrement in rectal temperature of normal subjects in air temperature at 4 C (40 F) with water temperature of the same value[82] No diminution in rectal temperature was observed in subjects exposed to air after one hour Those exposed to water on the other hand experienced a decrease as great as 7 C (12 F) in body temperature Although there are great differences in the rate of cooling of human beings in air and in water these are not explained entirely by a difference in physical heat conduction by the two media Men exposed involuntarialy to air temperatures usually are clothed and the protection provided by garments is considerable Following immersion all clothing except impermeable items become wet rapidly and approaches the temperature of the water Furthermore heat loss from the medial aspect of the legs and arms is less than the loss from peripheral portions of the body during immersion It is con

The formed elements of the blood as well as the chemical constituents undergo considerable change in concentration Hemoconcentration follows decrease in blood volume and the circulating red blood cell count and serum protein content may be increased as much as 5 per cent A shift of fluid from the blood to tissue cells when the protective reflexes are maintained, has been observed in man by Talbott[11] and in animals by Barbour and associates and by Conley and Nickerson[6] Analysis of tissues shows an increase of water and potassium content and a decrease of sodium There is a reversal of this shift as hypothermia persists and neuromuscular depression develops Tissues lose fluid to the extracellular spaces, visible edema develops and concentration of hemoglobin and proteins in the circulation blood falls below normal These changes may persist during and for a short time after restoration of body temperature

The white blood cell count increases significantly with a rise in percentage of polymorphonuclears and percentage of reticulocytes The sedimentation rate and platelet count decrease Within forty eight hours after restoration of body temperature, the sedimentation rate is normal[7] Discordant variations in concentration of non-protein nitrogen of the blood have been reported Some investigators have observed an increase, others a decrease[78] Examination of the arterial blood for concentration of oxygen and carbon dioxide shows a significant acidosis with a reduction in alkaline reserve by as much as 50 per cent This is associated with a shift in the oxygen dissociation curves to the left and a decrease in alveolar pO_2 so as to maintain normal arterial saturation with oxygen[9] Respiratory regulation remains effective at 25 C in spite of poor diffusion of gases in the lungs Routine urine analyses for albumin, sugar and formed elements are negative

Determination of oxygen consumption shows an increased energy exchange prior to neuromuscular depression and a metabolic rate as great as 40 per cent below normal after neuromuscular depression[7] Shivering involuntary activity and muscle rigidity are thought to be responsible for the increased exchange Although Fay observed a disappearance of shivering, when the rectal temperature fell below 32°C (90 F), this was not our experience when no drugs were given after the induction anesthesia We had visible evidence of shivering at temperatures below 27°C (80°F) just as animals have been noted to shiver at low body temperatures[67]. Shivering is less violent on the return toward normal temperature

Burton and Bronk[21] have described the muscle tremors in the

reaction of cold upon the brain but rather to failure of the oxygen supply mechanisms, i e circulation and respiration Irreversible damage probably is due to anoxia of the central nervous system resulting from this failure Events that contribute to death in persons with reduced body temperatures as a result of accidental exposure to cold are many One factor that has been stressed recently by Adolph and Molnar is general bodily fatigue that accompanies prolonged shivering Since shivering may persist for several hours even in persons that are actively moving about profound physical fatigue is inevitable Undoubtedly this augments the regressive processes and hastens the rate of development of hypothermia Mortality statistics from exposure to cold have been considered in a document prepared by the Metropolitan Life Insurance Company[8] Reported deaths from exposure averaged 363 per year during the period 1033-1940 Males outnumbered the females 4 1 A majority of the deaths in males occurred in persons 50 years or older The highest death rate per state was in Nevada where it was 24 0 per million The rate was 14 9 in Montana 1 6 in New York State and 0 7 in California

Pathological Effects

The line of demarcation between physiological processes and pathological changes pertaining to the effect of cold is not exact and some of the discussions in other sections of this chapter concern pathology or transitional changes from physiology to pathology Freezing immersion foot and trench foot will be discussed in this section Animal and human material has been available for morphological and biochemical study

Freezing—The freezing of a localized portion of skin or a larger area such as a limb of an anesthetized animal is accompanied by intense vascular constriction[88 89 90] Lange and Boyd[1] using the fluorescein injection technique under ultra violet light could demonstrate no circulation of blood for a period of from 30 to 1 0 minutes in frozen tissue of rabbits This was followed by an interval of several hours in which there was dilation of the vessels which in turn was replaced by vasoconstriction Biopsy at this time showed clumping of red cells in arterioles and capillaries Later true thrombosis was evident, and eventually gangrene developed Clumping thrombosis and gangrene could be prevented by the injection of an anticoagulant heparin, prior to freezing Redness persisted for 2 days and swelling for 4 or 5 days

cluded that heat loss in water is, at most, only 3 or 4 times that of air, but this difference may be near the critical range Survival under such circumstances may be determined by minutes of exposure rather than by hours

Wayburn[8] studied 6 aviators, who had bailed out and had been picked up in the English Channel The lowest rectal temperature at the time of the first observation was 24 C (93 F) This patient had been in sea water at 6 C (43°F) for 30 minutes He was in wet clothes for an additional 30 minutes before he was placed under medical care at this time he was comatose Cardiovascular observations by Wayburn showed auricular fibrillation, prolongation of the P-R interval, imperceptible radial pulse and a low blood pressure Each of these observations has been noted during experimental hypothermia The arrhythmia was attributed to vagal overactivity Blood studies revealed an increase in concentration of blood sugar and nitrogenous products in some instances During recovery there was a hyperpyrexia, some loss of memory loss of consciousness and irrational behavior Wayburn treated his patients with rapid warming, warm fluids by mouth and parenteral plasma He cautioned against the harmful effects of epinephrin The report by Alexander[31] of the Dachau experiments in Germany under Nazi authority gives data consistent with experimental and immersion hypothermia There was one survival with a minimum rectal temperature of 25 C (77 5 F) and several deaths with rectal temperatures between 27 and 29 C (88, 85 F) Rapid rewarming was found to be the most efficient form of restoration of body temperature It is believed that the beneficial effect of rapid rewarming of patients following hypothermia of short duration a few hours may be reconciled with the harmful effect of this procedure in patients following hypothermia of long duration one or more days A migration of fluid from the vascular bed in patients in the second category occurs Rapid rewarming under such conditions and before fluids can be replaced[3] merely aggravates the vascular shock

The mechanism of death in humans during hypothermia may be deduced with a fair degree of certainty Fuhrman and Field[6] determined the rate of oxygen consumption of slices of kidney cortex and cerebral cortex from the rat following exposure of the slices for 1 hour at -18 C (0.4 F) Normal oxygen consumption was observed when the tissues were returned to a temperature of 38 5°C (101°F) It was concluded that the death of an intact animal following hypothermia below the vital range is not attributable to the direct or irreversible

associated with complete necrosis No difference was observed between effect of chilling and freezing except in regard to degree of damage

Comprehensive pathological studies of one patient who died during experimental hypothermia have been reported by Talbott[71] The findings in this instance are of significance because the patient was suffering from schizophrenia only and not from any recognized disturbance beyond the central nervous system A minimal rectal temperature of 27 C (80 F) had been reached during hypothermia The internal temperature of the body remained below 37 C for 50 hours External heat was believed to have been applied too rigorously during restoration of temperature Cardiovascular collapse ensued and death followed shortly after The significant anatomical finding included patchy bronchopneumonia and slight degeneration of the cortical cells of the brain It was believed that the death followed cardiovascular breakdown and that no one of the morphological changes was independently responsible for death Of particular interest was the absence of pathological changes in the kidneys

Trench Foot, Immersion Foot Frozen Foot—Trench foot, immersion foot and frozen foot occur in different geographical areas but the symptomatology and pathology are essentially similar Trench foot usually develops in infantry men who have been fighting in wet terrain with air temperatures near freezing Immersion foot or immersion hand occurs at sea on life rafts at air temperatures that may be considerably higher Frozen foot is a malady of sub freezing and sub zero temperature A person afflicted with any one of these maladies during military operations usually is forced by circumstances to remain sitting in a relatively immobile position general body protection against the elements is inadequate warm food is unavailable usually change of clothing and footgear to warm dry items is impossible and the psychological situation is tense because life many times is at stake Moisture from the body or from the environment is present in excessive quantities The first symptoms of trench foot or immersion foor during the period of immobility whether it be in a trench a foxhole or on a life raft are tingling and a stinging sensation in the feet These are followed by numbness some tenderness but no pain and occasionally muscular cramps If boots are worn these become difficult to remove and once removed cannot be reworn because of swelling of the feet Trench foot usually takes several days to reach this stage but it may develop more rapidly On the other hand exposure on a raft for not more than 1 hours may be sufficient to produce immersion foot[8,91]

Vesicles appeared on the toe pads, and subcutaneous hemorrhages were observed in some animals, particularly those which had not received an anticoagulant. The exposed legs of all untreated rabbits began to show necrosis 4 days after freezing. Gangrene was complete within 10 days. All of the animals showed motor paralysis and sensory disturbance immediately after exposure. The damaged legs dragged when the animals walked, and the reaction to pinprick was diminished or absent. The animals which had received an anticoagulant, showed such abnormalities for 3 or 4 weeks, those, which had not been treated exhibited them until gangrene developed.

Morphological study of the tissues of the untreated animals showed a predominant vascular reaction. Gram positive cocci were present in deep and superficial tissues. Granular precipitated protein substances, strands of fibrin and moderate number of red cells and leukocytes were scattered throughout the edematous tissue. No degeneration of muscle was noted 2 days after exposure. Circumscribed infarcts and necrotic plugged vessels were seen among the dead muscle fibers 6 days later. Necrotic areas of fat appeared in the same sections. All the small vessels were dilated, packed with erythrocytes and as prominent in section as if they had been injected for special purposes of demonstration. The vessel walls showed a hyalinized homogeneous appearance. Red cells had entered the walls and adventitial sheaths.

Several investigators have[88, 9] studied the functional effects of the freezing of the extremities of dogs. A decrease in plasma volume, an increase in hemoglobin content and a decrease in total circulating plasma proteins were observed as in hypothermia in humans. A marked drop in blood pressure was associated with the thawing of a frozen extremity. Obvious swelling of the affected limb was accompanied by a decrease in total extra cellular water. These changes were interpreted as associated with a migration of fluid and protein from the blood into and about the tissue cells of the frozen limb. The protein content of edema fluid approached that of serum[88]. The lipid content of the zona fasciculata of the adrenal cortex was markedly decreased[9].

Denny-Brown and associates[93] observed the effect of cold upon the exposed nerve trunks of the cat. The myelin and axis cylinders of the peripheral nerves were damaged selectively, the larger the trunk the greater the damage. Damage was produced by exposure to temperatures as high as +8 C (46 F) for intervals as short as 30 minutes. Necrosis of whole nerve bundles followed freezing. Regeneration was rapid and complete subsequently in all grades of injury except that

The end results in mild cases are satisfactory and apparently there is complete recovery[86] In the more severe cases there may be recurrence of *pain tingling and swelling especially on walking prolonged standing* or exposure to cold Deep seated aching pain persists in a few instances and may be associated with tenderness in the joints usually the first metatarsal phalangeal joint or may be localized deep in the arch of the foot Limitation of motion in this joint muscle weakness and wasting and difficulty in walking have been reported Some complain of hyperhidrosis of the feet and of anesthesia and paresthesia in the tips of the toes The late pains the paresthesias and the rigidity of the affected parts may be due to compression of nerve endings and infiltration of muscle bundles with scar tissue Osteoporosis has been demonstrated and appears as diffuse or localized areas in the distal portion of the metatarsals and in the proximal portion of the phalanges Occasionally the extremities may become excessively sensitive to cold so that symptoms simulating Raynaud s disease may persist for hours after a return to a warm environment The foot may be sensitive to heat as well as to cold This instability of temperature may not be accompanied by any apparent change in the appearance of the feet or by cyanosis Foot deformity appears occasionally The longitudinal and transverse arches disappear, and the great toe contracts in semi dorsiflexion

Comprehensive studies of the pathology of trench foot[87] and immersion foot[9] have now appeared The morphological structures in each condition are similar Most tissues of the affected parts are involved In the early cases there is edema intracutaneous hemorrhage and necrosis in the stratum corneum of the skin In late cases there is little epithelial proliferation at the edges of the ulcerated areas The sweat glands in the early cases show cellular degeneration and the vascular plexus surrounding the glands is comprised of dilated and engorged channels, some of which are thrombosed The collagen of the dermis is necrotic Clumped red cell masses fill the dilated blood vessels in the dermis Cellular infiltration is evident throughout Increased vascularity congestion and hemorrhage characterize many regions with large collections of hemosiderin laden macrophages The subcutaneous fat shows infiltration with leucocytes and the interlobular fibrous septa show edema and leucocytes Foam cells filled with finely divided fat infiltrate the fat lobules diffusely Actual fat necrosis is unusual except in the mummified areas Considerable fibrous replacement of adipose tissue is apparent

Prolonged dependency of the feet, tight fitting boots and previous foot trouble augment the inevitable pathological changes Walking frequently is difficult during the exposure stage, and when walking is necessary, the afflicted complains of ataxia and the feet feel like blocks of wood Undoubtedly any walking at this time increases the damage to affected tissues There may be a stocking type of anesthesia varying from hyperesthesia and hypalgesia in mild cases to complete loss of all forms of cutaneous sensation, pain, touch and temperature, respectively in severe cases Pulsation is absent in the peripheral arteries, and cutaneous circulation appears to be sluggish The skin may be pale, waxy white, mottled blue or purplish in color

When a patient so afflicted is removed to a warm environment, the foot develops a bright red flush, and the pulsations become full and bounding These findings are identified with the hyperemic stage and may last *for a few days or even a few weeks Swelling increases rapidly* and the feet become hot and dry Blisters blebs ecchymoses and areas of gangrene appear shortly Damage is greatest in the toes the distal part of the dorsum of the foot and the ball of the foot, respectively The patient is toxic restless and is in need of heavy sedation Pain is severe in all except the mild cases, is burning or throbbing in character and increases in intensity for one or more days Ungley[9] has described another type of pain which may appear a week or more after treatment has begun This is shooting or stabbing in nature It begins in the ankle joint or in the midtarsus and radiates to the tips of the toes It is described as similar to the lightning pains of tabes dorsalis It is aggravated by heat and relieved by cold It is most severe when the feet are dependent after exercise Although this pain may disappear within a period of from 2 to 4 months it is not uncommon for it to be present a year or more after injury Edema which may extend as high as the knee usually subsides before the 10th day Ankylosis may develop and appears to coincide with sensory loss The superficial layers of the skin gradually mummify and desquamate leaving a pink sensitive skin Dry gangrene of the toes appears finally Complications include localized infection, cellulitis lymphangitis and septicemia Phlebothrombosis of the veins of the leg and particularly of the dorsum of the foot and along the course of the saphenous veins has occurred and may be associated with petechiae in the skin Transient hematuria and albuminuria, enlargement of the liver and mild febrile reactions have been observed in patients with immersion foot but not in those with trench foot

comes suffused and red upon return to warm environment Tingling and paresthesia may persist for one or two days and the affected parts may desquamate eventually

There is no method of *treatment of frostbite* that is accepted generally Rapid warming as well as slow warming has been recommended The temperature change may be less important than the application of other measures Parts should not be rubbed with snow or any harsh substance Infection should be avoided by judicious local handling as well as by the use of antibiotics Elevation of an extremity during the healing stage is necessary Application of grease and oils to the face hands and feet has been recommended for prophylaxis against frostbite There is little evidence that this is effective On the contrary when grease becomes incorporated in clothing as it is apt to following its application to the skin the insulating value of the protective clothing is diminished and harm rather than benefit follows Once a member has been frostbitten it is presumed to be more susceptible to cold

Acclimatization

The evidence in support of acclimatization of man to heat is convincing it is less so in respect to cold Nevertheless there are several factors that presumably are integrated and make adjustment in a cold environment possible Some are undoubtedly physiological others are physical Thus a person habituated to cold weather undoubtedly clothes himself more efficiently and makes greater use of the same items of apparel particularly in regard to protection against wind and disposition of moisture The type of food eaten may also be a factor Fat persons are assumed to be more resistant to cold than lean persons a fact which has been attributed to an effective insulating layer of fat under the skin Persons who are born and live in warm climates seem less able to withstand cold weather than those who have experienced little else but cool or cold weather

Physiological adaptation may be separated into a rapid and a slow phase The rapid phase is characterized by vasoconstriction and decreased heat loss which begins as soon as the temperature of the skin encounters an environmental temperature below the comfort zone The second phase follows immediately after the first and may not be complete for several weeks Bazett and associates[49] observed a relatively slow decrease in blood and plasma volume and an increase in concentration of serum protein and blood hemoglobin Vasoconstriction likewise may not

Marked engorgement of the vascular tree is seen in the early cases All of the vascular channels stand out in sharp relief Extra-vascular red cells surround the engorged plexuses Fibrinous thrombi as well as clumps of red cells are observed diffusely throughout veins and arteries in some sections Hemolysis is present in others Later stages show changes similar to those of endarteritis obliterans with complete obliteration of the lumina The muscle fibers show degeneration necrosis and cellulitis, followed by extensive atrophy and fibrosis Tendon sheaths have exudative and proliferative lesions with prominent masses of fibrin The nerves show areas of edema and inflammation Demyelinization is marked Between the fibers there are fat containing cells from the devitalized myelin Study of the bony structures shows osteomyelitis and an inflammatory exudate which undermines and invades the cartilage Osteoporosis may be sufficiently marked so that the bones cut readily with a knife Edema, serous exudation cellular infiltration, vacuolization and myxomatous degeneration are seen in the marrow

The *treatment of immersion foot*[94] or *trench foot*[98] is based upon conservative measures aimed to reduce the metabolic demands of the part until edema subsides extravasated blood and proteins are absorbed and vasomotor tone re-established The afflicted should elevate the feet and seek hospitalization as soon as possible after trench foot is suspected The limbs should not be rubbed or massaged Strict asepsis must be maintained and antibiotics should be administered The feet should be exposed to moderately cool room air (20 C) Application of heat to the extremities is inadvisable at any stage of recovery All local applications to the affected skin should be avoided except possibly cold Ice bags are indicated and may be continued for several days in severe cases with intense hyperemia and severe neuritic pains[9] Buerger's exercises are of value after hyperemia and edema have subsided Physiotherapy, also may be indicated at this stage of recovery Sympathectomy is to be considered only in cases in which there is objective evidence of circulatory insufficiency or in which manifestations resembling Raynaud's phenomenon develop and persist for months or even years[9, 90]

Frostbite —Frostbite due to freezing of tissues may be observed on parts of the face or head or on hands or feet Prolonged exposure to very cold temperatures usually is the offender in humans Sub zero temperatures with a high wind blowing on a poorly protected person for only a short period of time may lead to frostbite of the skin over the malar prominences nose or ears Inspection of the site of frostbite reveals a pearly white area surrounded by pale pink skin The white area be

comes suffused and red upon return to warm environment Tingling and paresthesia may persist for one or two days and the affected parts may desquamate eventually

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be maximal for sometime. Total body water is decreased during this period. Kidney excretion is augmented and cardiac output and blood pressure are diminished. Heat exchange is modified also following exposure.[illegible] Contact with a cold environment is accompanied by an initial decline in rectal temperature, which is restored after a few days. Evaporative heat loss declines rapidly at first, then slowly, and after a few days gradually returns to normal. Radiation and conduction undergo a rapid increase initially, followed by a more gradual change. Evidence of delayed maximal acclimatization was reported by Glickman and Keeton.[illegible] The decrement in skin and rectal temperatures during 8 hour daily exposures did not become minimum until one month had elapsed.

NUTRITIONAL REQUIREMENTS

The dietary habits of dwellers in cold climates are concentrated upon fat and protein foods. Whether this preference is of teleological significance or merely one of availability has not been established. Thomas[10] maintains that absence of carbohydrates from the diet of Eskimos is nothing more than an expression of the small amount of carbohydrates at hand. Controlled studies in support of dietary preferences have been confined largely to animals. LeBlond and Dugal[103] exposed albino rats to a temperature of −2 C and noted the free selection of carbohydrates, fats and proteins. The greater the amount of fat consumed and the smaller the amount of carbohydrate, the higher was their tolerance to cold as measured by body weight changes and percentage survival.

The effect of cold upon nutritional requirements in humans has been investigated extensively by Glickman, Keeton, Mitchell and associates.[101,104,10] They observed groups of men over a period of several months who were exposed for 8 hours daily to an environmental temperature of −29 C (−20 F) with considerable protective clothing or to an environment of 16 C (60 F) with little protective clothing. The remainder of the day the experimental subjects lived in an average environmental temperature 23 C (73 F). The subjects wore arctic Army issue clothing during the cold room exposure (−29 C). The effect of proportionate amounts of protein, fat and carbohydrate in the diet as well as other modifications was studied. The ability to withstand exposure to such a degree of intense cold as well as psychomotor functions could be modified considerably by the composition of the diet and the time interval between feedings. The subjects on a high carbohydrate diet (362-498 gm per 3,000 calories) required an average of 188 per

ent of food calories in relation to basal expenditure in order to maintain body weight Those on a high fat diet (45 gm per 3 000 calories) required oo per cent and those on a high protein diet (305 gm per 3 000 calories) required only 16 per cent The cooling of the internal tissues of the body on exposure to intense cold was greater on a high carbohydrate diet than on a high fat diet but only when the interval between meals was reduced to 2 hours No difference in the cooling of the skin was noted between a high fat or a high carbohydrate meal The performance in selected psychomotor tests favored the high fat diet Decreasing the interval between meals exerted no favorable effect upon rectal temperature if the meals were largely carbohydrate On the other hand a favorable effect was demonstrated if the meals were high in fat It was concluded that a high fat diet enjoyed a slight preference over a high carbohydrate diet which in turn showed a significant advantage over a high protein diet

Small meals spaced at 2 hour intervals were found to be more favorable than larger meals at 4 or 6 hour intervals A comparison of the least favorable interval of feeding and type of food a high protein diet with a longer interval of feeding and the most favorable arrangement a high fat diet served at 2 hour intervals showed that the decrement in rectal temperature induced by cold could be reduced by two thirds and the decrement in general psychomotor function by one half The superiority of the high fat meal in maintaining body temperature was thought to be related to heat emission rather than heat production and presumably was associated with a temporary deposition of fat in the sub dermal tissues These findings substantiate the empiric observations that a high fat diet is desirable for cold weather operations although it is surprising that the specific dynamic action of proteins does not place this type of food above carbohydrates The effect of water soluble vitamins upon resistance of the body to cold was quantitated in another phase of the study Doses of ascorbic acid thiamine riboflavin and nicotinic acid above amounts required for adequate nutrition were without any measurable effect upon functions investigated

Resistance to Infection

Resistance to infection has been presumed to be lowered by exposure to cold but there is little controlled clinical evidence to support this belief[108] A change in vasomotor activity following exposure to cold drafts has been postulated Depression of ciliary activity[14] and drying of the

be maximal for sometime. Total body water is decreased during this period. Kidney excretion is augmented, and cardiac output and blood pressure are diminished. Heat exchange is modified also following exposure. Contact with a cold environment is accompanied by an initial decline in rectal temperature which is restored after a few days. Evaporative heat loss declines rapidly at first, then slowly and after a few days gradually returns to normal. Radiation and conduction undergo a rapid increase initially, followed by a more gradual change. Evidence of delayed maximal acclimatization was reported by Glickman and Keeton[101]. The decrement in skin and rectal temperatures during 8 hour daily exposures did not become minimum until one month had elapsed.

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in which 8 members in the family comprising 4 generations were studied for hypersensitiveness to cold and 17 were found to be afflicted These data lend support to the assumption that there are transmissible constitutional differences in regard to reaction to cold and that possibly it is a true allergic response

The reaction to be expected upon exposure of susceptible persons to cold is redness burning and urticaria These changes may appear upon exposed portions of the body in going out of doors in cold weather or experimentally following application of ice locally or ingestion of cold liquids and solids the body meanwhile remaining at room temperature The development of edema locally may be associated with an elevation of skin temperature In unusual instances there may be constitutional reactions in hypersensitive persons such as a significant decrease in blood pressure a rise in pulse rate flushing of the face vertigo or syncope[11] Attacks may be produced by cold blasts of air or by a sudden change from a warm to a cool environment Swelling of the lips or dysphagia may occur after ingestion of cold substances Other manifestations of an untoward reaction to cold include purpura hemorrhagica[116, 117] and paroxysmal hemoglobinuria the latter condition having been observed in two types of individuals Mure[118] was able to induce an attack of hemoglobinuria in a subject following exposure to a temperature of $-6°$ C (21 F) for one hour This patient had a positive Wassermann reaction and the Donath Landsteiner test was positive The patient no longer experienced hemoglobinuria on environmental exposure following anti syphilitic treatment

Bennins and Feasby[119] reported the findings on two patients who had powerful cold agglutinins in their serum Each had Raynaud s disease It was concluded by these investigators that the Raynaud s phenomenon was produced by increased sensitivity to cold of the digital arteries More convincing evidence was presented by Stats and Bullowa[120] from a study of cold hemoagglutinins associated with symmetrical gangrene of the tips of the extremities Agglutination of red cells in the veins followed exposure to cold The agglutinating effect was shown to reside in the patient s serum and not in the red cells The presence of cold hemoagglutinins was not explained although hemoglobinemia and hemoglobinuria were thought to be be caused by activation of these substances during environmental exposure Syphilis and hemolytic anemia were not believed to be responsible Two other instances from the literature of a similar type are discussed by them

Treatment of cold allergy has not been successful Desensitization to

mucous membranes[10] have been noted which may inhibit local tissue resistance to pathogenic organisms On the other hand, Smillie[109 109] has shown that in isolated communities near the Arctic Circle exposure to cold per se does not result in upper respiratory infections Pathogenic organisms disappear from the nose and throat of all the inhabitants a few weeks after they are isolated from the outside world by onset of winter

The evidence is equivocal in experimental animals Repeated reduction of body temperature, 4 to 8 C below normal, caused no apparent inhibitory or significant inciting effect upon experimental tuberculosis in guinea pigs which were injected subcutaneously with a standard strain of virulent human bacillus[100] Hypothermia had little or no effect upon subsequent bacteremia and death in rabbits infected with a virulent strain of type I pneumococcus On the other hand when a relatively avirulent type III strain was used the induced hypothermia resulted usually in overwhelming bacteremia and death It was concluded that resistance may be overcome by artificial reduction of body temperature and that interference by physical means with the normal febrile mechanism handicaps the nonspecific mechanism of the body Exposure of mice to 5 C (41 F) environmental temperature for 5 minutes after drenching with cold water did not alter their resistance to human influenza virus[111]

Acute glomerular nephritis has been associated with exposure to cold dampness and drafts in a subtle fashion Reflex vasoconstriction in the kidney has been demonstrated[112] following chilling of experimental animals Macleay Hall and Smith[113] exposed rats to a temperature of 5 C for ninety days and at pathological examination observed tubular necrosis and glomerular swelling

Hypersensitive Reactions

It has been shown conclusively that some persons are hypersensitive to cold The reaction is sufficiently disabling in a few instances so as to force the sufferers to modify their routine of living Duke[13] was one of the first of the group of contemporary internists to call attention to urticaria caused by cold and recommended a desensitization procedure as treatment Urbach and associates[114] differentiate cold allergy and cold pathergy ' and subdivide hypersensitization to cold into five categories as follows (1) primary physical allergy (2) production of secondary antigens in tissues by cold (3) release of histamine like substances in tissues (4) vasomotor neuropathy and (5) disturbance of the temperature regulating center An interesting family history is reported by them

In Psychiatric Disorders—Following the observation that hypothermia had an inhibiting effect upon the sensation of pain, its employment in the treatment of morphine addiction[1] and for dental anesthesia[1] was advocated Results in each instance were favorable Finally Talbott and Tillotson[66] in 1941 reported favorable results upon a series of patients suffering from schizophrenia Mo of the patients had been hospitalized for months or years and had been treated previously with insulin or metrazol or both without benefit Each of those who were older than thirty years and who had been confined to a mental hospital for more than a year showed little or no prolonged correction of their mental deficiencies On the other hand most of those who were younger than 30 even though they had been sick for as long as 3 years showed a significant alteration in their psychiatric responses Following these initial studies investigators in other mental hospitals became interested in the therapeutic possibilities of hypothermia The war interfered subsequently and to the author s knowledge this work has not been pursued elsewhere The induction and maintenance of a reduced body temperature in humans is an expensive and laborious procedure and associated with a definite risk Unless distinct advantages not inherent in other therapeutic procedures, are shown to exist such a technique will not be widely used

In Shock.—The treatment of shock medical or surgical has long included the application of heat to the body particularly to the extremities The application of heat with resultant vasodilatation does not follow sound theoretical principals however when the shock is associated with a diminution in circulating blood volume Hence a revision of thinking was inevitable and merit seemed to rest in the application of cold a vasoconstrictor in the treatment of shock associated with decreased blood volume Experimental studies on animals did not support such a reversal of physiological action however Blalock and Mason[13 14] exposed animals to cold and induced hypothermia as low as 4 C following venesection The application of cold did not increase the chance of survival but was accompanied by a lengthening of the survival time of animals with a low blood pressure Similar results were reported by Antos[1]

Cleghorn[16] investigated the survival of dogs following hemorrhage when they were exposed to one of 4 environmental temperatures Survival was maximum at an environmental temperature of . C (7. F) It was reduced when the environmental temperature was 11 C (52 F) and was minimal at temperatures of 29 or 35 C (85 95 F) Similar findings were reported by Ricci and associates[17] following traumatic

cold, as recommended by Duke, has helped some patients It may be necessary to abandon living in cool or cold climates and reside only where a high environmental temperature prevails throughout the year Some slight benefit from the use of anti-histamine substances (benadryl) has been noted[1] [1]

Therapeutic Uses of Cold

In Malignancy —Cold has been recommended for the treatment of medical, phychiatric and surgical conditions in recent years As noted in the Introduction this phase of the effect may be treated directly to the pioneer studies of Smith and Fay in the treatment of inoperable malignancies by prolonged hypothermia They were intrigued by the observation that primary and metastatic cancer rarely involves the parts of the body where reduced surface temperature prevails Thus the extremities usually are free of neoplastic tissue and enjoy a lower temperature than the breast or uterus, organs associated with higher tissue temperatures Although definite regressive changes in undifferentiated cell growths in deep metastatic lesions were not observed consistently by Fay and Smith lowering of the body temperature was followed by significant clinical changes Most important of these was relief of pain So successful was this effect that Fay[1] was able to eliminate the use of narcotics in the treatment of intractable pain, and operative intervention for pain no longer was necessary In selected instances patients who required one or more grains of morphine daily for control of pain before hypothermia, were quite free of pain without opiates for several weeks after A few patients were free from pain for as long as 4 months Regressive changes in neoplastic tissue was evident at microscopic examination in addition to the analgesic effect The response of sarcomatous tissue was less striking than that of carcinomatous tissue[2] The more undifferentiated the carcinoma the more rapid the regressive phenomenon Primary tumors as well as lymph nodes that were invaded underwent diminution in size

Local application of cold was used also in the treatment of cancer in various parts of the body Specially fitted coils, through which a refrigerant circulated were applied, and a skin temperature between 4 and 10 C (40-50 F) was maintained for days or weeks Impressive results were noted initially Contrary to the first hopes however neither local nor generalized application of cold is a cure for cancer Hence this therapeutic agent has been abandoned in most hospitals

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shock in dogs A maximum survival was noted at an exposure temperature of 20° C (68 F) On the other hand local application of ice to an injured limb afforded almost complete protection from death

These several series of well controlled studies on animals define the optimum environment for recovery from hemorrhagic or traumatic shock The temperature should be low enough to avoid peripheral vasodilatation but high enough to avoid significant losses of body heat The temperature range 20 to 24° C (68-75 F) is suggested as satisfying these requirements Additional blankets or application of heat defeats the purpose On the other hand local application of cold to a traumatized extremity may be of value

In Gangrene—The last condition to be discussed in which application of cold has been recommended is gangrene or impending gangrene of an extremity Allen[3] advised the immersion in ice following application of a tourniquet to a crushed, gangrenous or infected extremity that is to be amputated Approximately 3 hours of immersion are necessary for adequate anesthesia All sensation is abolished, and the sciatic nerve may be cut without pain Following operation with the aid of continuous cold, after pains are prevented or reduced so that sedatives are unnecessary The small variations in pulse and blood pressure during operation are ample evidence that shock has been avoided The otherwise inadequate blood supply and oxygen are ample to provide for tissue requirements because of reduction of metabolism locally Post operative thrombosis is reduced significantly Physiological confirmation of the validity of the procedure has been reported by Massie[1 8] He observed that living tissue remained viable when completely asphyxiated with a tourniquet for many hours, if the skin temperature was kept between 2 and 4 C (35, 40 F)

Acute circulatory accidents of the extremities with thrombosis or embolism may be controlled with the application of cold An ice pack without a tourniquet preserves the tissues of the extremity until collateral circulation develops following traumatic or arterial embolism The serious effects of immediate anoxia with tissue necrosis and gangrene is minimized Satisfactory results may be anticipated, if cooling is combined with the use of chemical anti coagulants Cold exerts a beneficial anti thrombic action also The spread of infection is affected by cold but not always in a favorable fashion During periods of low temperature resistance of cold tissues to infection is decreased Upon restoration of normal temperature however, infection may be augmented Normal healing may be delayed during exposure to the cold[1 9]

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CHAPTER XIX-C

THE DISTURBANCES ASSOCIATED WITH HIGH ALTITUDES

By Edward C Schneider

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Travel in high mountains and ascents to high altitudes by airplane or balloon place man's body in an abnormal environment which disables it in some degree and causes it to undergo certain adaptive changes to counteract the abnormality of the new environment That the body finds existence arduous and its efficiency impaired at high altitudes is evidenced by the symptoms experienced during an attack of mountain sickness and the paralysis experienced occasionally at great heights during airplane and balloon flights

The Causes of Altitude Effects

The causes of altitude disability have been variously designated Enthusiastic students have at one time or another attributed the action to each of the several climatic variables encountered at high altitudes such as diminished

atmospheric pressure low temperature and humidity, high winds electric conditions of the atmosphere, ionization of the air, and a low partial pressure of oxygen In the main there have been two schools, one that attributes the physiologic changes to altered action of mechanical factors and the other to altered action of chemical factors As early as 1878 Paul Bert[6] furnished clear experimental proof that the abnormal symptoms experienced by persons at considerable altitudes are due to imperfect aeration of the blood with oxygen This chemical theory did not at first find universal acceptance Later the Italian physiologist Mosso[7] developed the acapnial theory which attributed many of the symptoms to a lack of carbon dioxide in the body Still later the outstanding mechanical theory of Kronecker[8] explained mountain sickness as the result of a disturbance in the pulmonary circulation induced by diminished atmospheric pressure

At the present time one of the chemical theories is almost universally accepted and holds that the rarity of oxygen at high altitudes is responsible for the disability and adaptive changes experienced by man at those elevations The rarity of oxygen in the atmosphere causes a reduction of this gas in the blood and thereby a want of oxygen anoxemia in the tissues

The Sources of Oxygen

Since it is to be demonstrated that the influence of high altitude is caused chiefly by its effect on the oxygen supply of the body, it will be worth while to review briefly the role of oxygen in the body

An adequate supply of oxygen is necessary for normal life Among organisms the immediate cause of death of the body as a whole is practically always a want of oxygen Oxygen in some form is required by all living things whether they are aerobic or anaerobic in habit Higher organisms must secure it in gaseous form When the oxygen supply is insufficient ill effects soon occur Hence it appears that few things are of more importance in practical medicine than a knowledge of the causes and effects of want of oxygen

The source of the oxygen supply is the atmospheric air The per cent of oxygen in our atmosphere is practically the same wherever sampled whether on a high mountain in a mine over land or over water The following are the proportions of gases in the air oxygen 20 93 per cent carbon dioxide 0 03 per cent and nitrogen including other inert gases 79 04 per cent

The rate of passage of oxygen into living organisms into the blood and from the blood to the tissues is determined by the pressure the gas exerts rather than by the percentage of the gas in the atmosphere at any altitude In a mixture of gases as in atmospheric air, each gas exerts a definite pressure, known as the partial pressure which is proportional to the amount or per cent present In order therefore to know the partial pressure of oxygen at any altitude the barometric pressure must be obtained It is then a simple matter to find the partial pressure of oxygen since it is always 20 93 per cent of the atmospheric pressure

The relationship of barometric pressure and the partial pressure of oxygen at high altitudes is illustrated in the following table

Altitude	*Barometer*	*Partial pressure of oxygen*
Sea level	760 mm	159 mm
10 300 ft	506 mm (2/3 normal)	106 mm
18 000 ft	380 mm (1/2 normal)	80 mm
28 000 ft	253 mm (1/3 normal)	53 mm
40 000 ft	148 mm (normal)	32 mm

While the atmospheric air is the original source of oxygen man and other mammals draw the oxygen which they use from the alveolar air of the lungs The dry alveolar air for man at sea level contains from 13 5 to 15 per cent of oxygen and 4 5 to 6 per cent of carbon dioxide Since the air in the lungs is ordinarily saturated with water vapor the pressure this exerts which is 47 mm is first deducted from the barometric pressure before the partial pressure of oxygen and other gases is calculated When this is done it is found that the partial pressure of oxygen in the alveolar air of man at sea level ranges between 96 and 107 mm

The alveolar air pressure of oxygen can be roughly approximated for altitudes above sea level In acclimatized persons it is always about 33 per cent less than the partial pressure of the oxygen of the atmospheric air for any given altitude

The Demand for Oxygen

The energy of the body is derived from the potential energy of food The quantity of oxygen required by the body is determined by the rate of metabolism The amount of oxygen needed in metabolism depends upon the chemical composition of the material that is being burned in the organism The seat of oxidation is in the living cell

It was formerly maintained that some organic substances were oxidized in the blood plasma and lymph Benzylic alcohol and salicylic aldehyde are substances that may be easily oxidized to their respective acids Now if either is introduced into blood plasma or lymph it is not oxidized but is quickly oxidized in the presence of fragments of living tissue The living cells of the tissue use oxygen by virtue of their metabolism There is no instance in which it can be proved that an organ increases its activity under physiological conditions without also increasing its demand for oxygen

An important question has been Is the quantity of oxygen taken up by the cell conditioned primarily by the needs of the cell or by the supply of oxygen? The answer has been that provided the supply is adequate the cell takes what it needs and leaves the rest The activity of organs is regulated by the central nervous system and by certain hormones The demand for oxygen is therefore determined by these two agencies

The Capacity for Storing Oxygen

The process of oxidation, as stated before, occurs within the living cell and is brought about by an enzyme Probably the first step in the use of oxygen is the formation of peroxide e g, hydrogen peroxide, by the enzyme So at any given moment there will be a certain amount of available oxygen present in the cells of the body as peroxides But the amount of these must be extremely small

At one time it was thought that the cell contained a store of intra molecular oxygen in loose combination However, when living tissue such as a muscle is placed in an atmosphere of pure hydrogen, even though it may respond to stimuli for awhile, the process of combustion does not go on, in other words there is no oxygen present in a form available for oxidation A very small amount of oxygen may exist in cell fluids in ordinary solution

In man the blood is practically the only storehouse for oxygen and its capacity is definitely limited The body lives a "hand to mouth existence with respect to its oxygen supply An ordinary sized man may have 4000 c c of blood in his body If its hemoglobin content is 14 per cent, 14 to 16 9 being normal then with the saturation of the entire volume of blood the store of available oxygen would be 740 c c Even at rest the body uses from 200 to 250 c c each minute One gram of muscle uses 006 c c of oxygen per minute when at rest and 08 c c or about 13 times as much, when in active contraction A gland uses 03 c c per gram of tissue during rest and 0 1 c c when active thus *increasing its usage threefold*

In the order of their oxygen need per gram the tissues rate as follows glandular muscular, connective, and nervous Little is known of the oxygen requirements of nervous tissue It may be above that of connective tissue

Inadequate Supply of Oxygen

The activity of the tissues is affected in several ways by a reduction in the oxygen supply Glandular tissues maintain their rate of metabolism, and therefore their consumption of oxygen as the supply is reduced even down to a very low pressure of oxygen The activity of muscular and nervous tissue is reduced as the available oxygen supply lessens On the other hand the kidneys are said to increase their metabolism when under low oxygen

Oxygen want in higher organisms means a slowing down of life at least temporarily Later this may be offset by compensatory reactions which finally supply the required amount of oxygen A condition in which the rate of supply of oxygen to the tissues by the blood in the systemic capillaries is insufficient for the normal activities is called anoxemia It is a condition that is very common and often dangerous in such diseases as pneumonia bronchopneumonia bronchitis asthma and many chronic cardiac cases In all of these and others the transport of oxygen is inadequate

Anoxemia may be acute or chronic An example of the acute form is obtained in airplane flights to very high altitudes and also in carbon monoxide poisoning Chronic anoxemia occurs in people who live at altitudes of 14 000 feet and above and in some cases of anemia and chronic heart disease

The Types of Anoxemia

Anoxemia may be divided into four main types which arise from four quite different groups of causes Anoxemia occurs (1) when the arterial blood is imperfectly saturated with oxygen this is known as anoxic or arterial anoxemia ( ) when the blood is deficient in oxygen carrying capacity this is known as anemic anoxemia (3) when the blood flows too slowly to supply the need of the tissues with oxygen this is known as stagnant or venous anoxemia and (4) when the hydrogen ion content of the blood is very low as a result of which the blood holds on to the oxygen too firmly this is acapnial anoxemia

In the anoxic or arterial type of anoxemia the pressure of oxygen in the blood is too low Consequently the arterial blood is not saturated to the normal extent and the blood is darker in color than it should be In this type there occurs faulty oxygenation of the blood in the lungs (1) because of a low oxygen tension in the inspired air examples of which are found in the aviator during flights to high altitudes and in the mountaineer or (2) because of irregular distribution of the freshly inhaled air as in shallow breathing emphysema bronchitis and asthma or (3) because of swelling exudates or other abnormalities in and around the alveolar walls which prevent rapid diffusion of oxygen into the blood as in the effects of lung irritant gas poisoning pneumonia and edema

In the an mic type of anoxemia the quantity of functional hemoglobin is too small *either the total amount is far below normal or a portion has been rendered* useless for the transport of oxygen The oxygen pressure the saturation of the blood and the color of the blood as it leaves the lungs are normal Anemia sometimes gives the conditions necessary for the first of the above causes Unless such blood circulates more rapidly than normally or gives up more than the usual amount of oxygen the tissues will be inadequately supplied Carbon monoxide poisoning is an example of the second cause of anemic anoxemia The molecular affinity of hemoglobin for carbon monoxide is about 99 times greater than its affinity for oxygen Hence a very small proportion of carbon monoxide in the air is capable of saturating the blood to a noticeable extent

In the stagnant or venous type of anoxemia the blood and its oxygen content are normal but the flow of blood is not rapid enough to supply the oxygen needed by the tissues In passing through the capillaries the blood may be more completely reduced than normally but even then the supply of oxygen to the tissues is insufficient Illustrations of this type are seen in shock after hemorrhage and in certain cases of cardiac disease

In the acapnial anoxemia the hemoglobin and oxygen content of the arterial

blood are normal, but the oxygen is held firmly by the hemoglobin because too much carbon dioxide has been lost from the blood and the blood has been rendered too alkaline Such a condition may result from forced breathing as follows from pain in certain severe injuries

The impaired efficiency experienced at high altitudes, is chiefly the result of anoxic anoxemia but at the beginning may be in part, the result of a temporary acapnial condition Barcroft has pointed out that the anoxic type of anoxemia is the most serious and difficult with which the body must contend It places the tissues at the greatest disadvantage as regards the oxygen supply, since the flow of oxygen to the tissues is proportional to the partial pressure of oxygen in the blood

It is important to appreciate that while we know something of the oxygen needs of tissues and how they obtain this gas we know almost nothing of their sensitiveness to a lack of oxygen Experience shows that many of the organs of the body can be revived hours after complete deprivation of oxygen Probably the nervous tissue even though its oxygen requirement is small is the most sensitive to a deficiency of oxygen and the most quickly killed by a complete lack of this gas It has been reported that cerebral cells can not be revived after eight minutes of complete deprivation of oxygen, the cerebellar cells after thirteen minutes the medulla oblongata cells after twenty to thirty minutes, and the spinal cord cells after forty five to sixty minutes

Altitude Disturbances Experienced During Airplane Flights

The behavior of the organism to the oxygen deficiency of high altitudes depends upon four conditions, (1) the speed of the ascent, (2) the height attained (3) the length of the flight and (4), to some extent, upon the physical condition of the body

It is difficult to make satisfactory physiological observations during a flight in an airplane because of the cold and wind The aviator himself does not make a good observer His attention to the technical and other duties of a flight diverts his notice from physical symptoms unless they become very unpleasant Further it is well known that one of the most outstanding effects of oxygen starvation is a dulling of the intellect and an unwarranted sense of well being and security

One hundred of the American aviators who had been in active service at the Front during the war when questioned regarding discomforts of altitude replied as follows 32 per cent declared they had never suffered any inconvenience 18 per cent that they suffered from shortness of breath alone, 10 per cent from cold and shortness of breath 2 per cent from headache and shortness of breath 6 per cent from headache and 12 per cent from feelings of physical exhaustion and mental depression These men were practically immune from the high altitude effects in that they remained in the air for so short a time

Even an experienced clinician or physiologist will as a rule fail to notice altitude effects under 10 000 feet but will find them evident at 1 000 feet From an altitude of 12 000 feet up to 25 000 feet the following symptoms may occur though it should be noted that no symptom or group of symptoms is universal

Headache —This is usually frontal and often sudden in onset It occurs ordinarily during first flights to great heights Repeated high flights often render the flyer more or less immune Headache is a frequent after-effect of anoxemia that occasionally persists for hours

Breathlessness —This is of common occurrence but varies in degree Very few aviators breathe through the nose when above 12 000 feet Breathlessness is exaggerated by muscular exertion and by cold

Muscular weakness —This is reported by Army aviators who have found it difficult to manipulate a camera or gun when above 15 000 feet Experience in a low pressure chamber and with low oxygen by the rebreathing method show that associated with weakness may be coldness of arms and legs numbness of the limbs or a feeling of the absence of these appendages At greater altitudes this condition gives way to a muscular paralysis

Periodic breathing —This is quite like Cheyne Stokes breathing It has been reported for altitudes of 18 000 to 20 000 feet and has been so annoying as to prevent the pilot from keeping his controls steady

Sleepiness —The flyer gradually becomes dull and sleepy he has no distress and becomes inefficient so insensibly that he does not realize his condition It is probable that aviators who claim to feel perfectly fit at high altitudes may in reality have been quite inefficient and sleepy This is a common condition in anoxemia as experienced in the low pressure chamber

Impairment of intellect and judgment —The effects of altitude on the aviator come upon him unawares There is first stimulation and a feeling of well being As the anoxemia develops the power to attend to stimuli diminishes even though perception yet remains efficient The mind may become possessed of some idea to which it persistently reverts The individual seems unable to act on knowledge that he may have because his mind is unable to initiate necessary action Birley[7] reports an interesting case of a pilot who met an enemy patrol at 18 000 feet He did not realize his danger but waved his hand to them in spite of the protests of his observer

Impairment of vision and hearing —These also develop gradually and unawares In the beginning noises are distinctly heard and the field of vision is large and bright Gradually the noise is tempered and may begin to recede the field of vision likewise grows gradually less bright and smaller Major Schroeder s report[1] of one of his altitude flights contains the following When I reached 25 000 feet I noticed the sun growing dim I could hardly hear my motor run and I felt very hungry He then thought to take oxygen and remarks and as soon as I started to inhale the oxygen the sun grew bright again my motor began to exhaust so loud that it seemed something must be

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efficiency However it is clear that some because they become mentally in efficient at only moderately low oxygen can not be trusted to fly at altitudes as high as 14 000 feet The altitude classification test shows that in these men the adaptive mechanisms either fail entirely to respond to the stimulus of lack of oxygen or respond very inadequately

Among the fainting type of reactors the lower brain centers which control the rate of heart beat the diameter of the blood vessels and the rate and volume of breathing are the first to be paralyzed by a lack of oxygen hence in many of these men early failure of the circulation and respiration occurs The altitude classification examination indicates that the fainters may be sub divided into three subgroups depending on which of the above brain centers is first seriously affected

In a large number of the fainters the arterial blood pressure falls first indicating a failure of the vasomotor center In some of these the systolic pres sure begins to fall first in a larger number the diastolic pressure falls first while in others the two pressures fall together If pure oxygen is administered while the arterial pressures are falling the process is immediately checked the vasomotor center again takes command and fainting is avoided In the second subgroup the approach of fainting is first indicated by a sudden and usually rapid slowing of the pulse rate It has been proved that this is brought about in two ways first by a stimulation of the cardio inhibitor center and second by a direct effect upon the pace making tissue of the heart In the third subgroup the approach of fainting is shown in a sudden decrease in the minute volume of breathing due no doubt to the fact that the respiratory center is being paralyzed by the lack of oxygen The individual members of the two types of reactors fainting and non fainting vary among themselves in ability to tolerate high altitudes As a group the fainters are least fitted for high flying When carried to the state of unconsciousness the non fainter re vives more quickly when given oxygen A comparison of the two groups studied by the altitude classification test is given in the following table which shows the altitude or percentage of oxygen at which the men became wholly in efficient

Lowest oxygen tolerated in per cent	Corresponding altitude in ft	Percentage of non fainting group that became inefficient	Percentage of fainting group that became in efficient
11–12	15 000–17 000		0 7
10–11	17 000–19 500	0 6	0 7
10–9	19 500–22 000	1	13 0
9–8	22 000–25 000	13 0	30 9
8–7	5 000– 8 000	40 1	41 7
Below 7	above 28 000	45 2	13 0

It would not be advisable for one to attempt to fly too near the altitude at which he tends to become unconscious In general it may be stated that the

wrong with it I was no longer hungry and the day seemed to be a most beautiful one'

Fainting — We have met several flyers, with long experience at the War Front, who believed that if an individual makes frequent flights to high altitudes he will sooner or later faint while in the air Dizziness and faintness have frequently been reported The tendency to faint, as seen during the war developed as the aviator became physically stale

The insidious action of altitude was nicely demonstrated in a balloon flight in 1862 made by the well known meteorologist, Glaisher, and his assistant Croxwell (see Haldane [13]) Glaisher first noticed, at an altitude of about 26 000 feet that he could not read his instrument properly Shortly after this his legs were paralyzed and then his arms though he could still move his head Then his sight failed entirely and afterwards his hearing and he became unconscious His companion meanwhile found that his arms were paralyzed, but that he was still able to seize and pull the rope of a valve with his teeth this permitted gas to escape so that the balloon descended As Glaisher recovered consciousness, he first heard his companion s voice and then was able to see him after which he quickly fully recovered

Tissandier [6] the sole survivor of a party of three, in a fatal balloon ascent in 1875 wrote At 24,600 feet the condition of torpor which overcomes one is extraordinary Body and mind become feebler little by little, gradually and insensibly There is no suffering On the contrary one feels an inward joy There is no thought of the dangerous position one rises and is glad to be rising The vertigo of high altitudes is not an empty word, but so far as I can judge from my own experience this vertigo appears at the last moment and immediately precedes extinction, sudden, unexpected, and irresistible

Types of Reactors Among Aviators

By means of the rebreathing altitude classification test used in the army it is possible to learn how soon the lack of oxygen begins to affect the individual and to find the type of reaction normal to the person This test has shown time and again that the subject may become absolutely inefficient and utterly neglect his task, and yet insist, when restored to fresh air that he was working perfectly and that there was no necessity for discontinuing the experiment

Schneider and Truesdell [3] have analyzed the records of 1050 altitude classification examinations and found that 47 per cent of the aviators were liable to faint at high altitudes while 53 per cent would be likely to react as did the meteorologist, Glaisher In this latter group the non fainting the higher or psychic, parts of the brain are paralyzed before the vasomotor, cardiac and respiratory centers Most of the men of this type when under low oxygen, can be carried into unconsciousness and will sit for awhile perfectly erect, glassy eyed deaf, and irresponsive to signals and questions A large proportion of these men tolerate anoxemia to very high altitudes without a marked loss of

Frequently the patient does not develop distressing symptoms until toward evening or during the night of the first day The next morning he may feel slightly giddy on arising from bed and any attempt at exertion increases the headache His face appears slightly cyanosed the eyes look dull and heavy and there may be a tendency for them to water The tongue is furred and the pulse is rapid usually in the neighborhood of 100 or over The temperature is sometimes slightly above normal or even subnormal The patient may feel cold and shivery The appetite is lost Periodic breathing often occurs During the second day these symptoms may begin to subside and entirely disappear in a few days

*There are wide divergencies from this slow or normal type of mountain sick*ness which have been grouped into two classes by Ravenhill[27] In the first cardiac symptoms and in the second nervous symptoms predominate Neither is common The cardiac type is well illustrated by one of Ravenhill s cases This man ascended from sea level to 15 400 feet in 42 hours He seemed in good health when he arrived he kept quiet ate sparingly and went to bed early but awoke the next morning feeling ill with symptoms of the normal type Later in the day he began to feel very ill In the afternoon his pulse rate was 144 and respiration 40 Later in the evening he became very cyanosed had acute dyspnea and evident air hunger all the extraordinary muscles of respiration being called into play His heart sounds were very faint the pulse irregular and of small tension thus presenting a typical picture of a failing heart The condition persisted during the night he coughed up with difficulty and vomited at intervals He was sent down on an early train the next morning At 1 000 feet he was considerably better and at 7 000 feet he was nearly well Ravenhill thought he would have died had he remained at the high altitude another day Ravenhill reports two more cases of the cardiac type who died during the attack

The nervous type according to Ravenhill in its simplest form consists of a feeling of nervous excitation and buoyancy Some feel as though they were being lifted into the air There may be twitching of the lips and trembling of the limbs In his most severe case there followed violent spasmodic movements of the limbs and sometimes typical convulsions

Other factors than the reduced oxygen tension of the atmosphere appear to hasten the onset and exaggerate the symptoms of mountain sickness More individuals are affected during bad than clear weather This is partly due to a depressing effect of weather on the body and partly to the fact that during bad weather the barometric pressure is lower than ordinary Alcohol hastens and increases the symptom because of a change in the circulation that directs the blood to the skin and lessens its flow to the brain Food also may precipitate an attack by diverting too much blood to the digestive organs Severe fatigue may make an attack of mountain sickness dangerous Reference has already been made to the influence of the topography such as gullies ridges and fields of snow

altitude limit of consciousness for unacclimatized persons is near 5,000 feet

Mountain Sickness

The first effect of altitude anoxemia on those who ascend mountains is often stimulating The traveler feels unusually well and exhilarated and often becomes talkative, unreasonable or quarrelsome Later, mountain sickness may occur

Since individuals differ in physical development and in power of adjustment to changes of environment it is found that mountain sickness befalls some at a lower and others at a higher altitude but it is also certain that no one who proceeds beyond a certain elevation the critical line for him escapes the malady An elevation of 10 000 feet, or even less provokes it in some, others escape the symptoms up to 14 000 feet, while only a very few possessed of unusual resisting power withstand to 19,000 feet The appearance of the symptoms of mountain sickness depends not only on the nature of the individual and his physical condition but also on various intricate contingencies, especially on the amount of physical exertion made in the ascent whether by climbing or by passive carriage on horse railway train, or automobile If the ascent is slow as on foot one is more liable to be attacked when climbing in gullies and on snow than on open ridges and rock However, on heated rock the condition may be reversed in that heating causes expansion of the air and therefore, rarefaction

The bodily disturbances brought on by residence at high altitudes may be characterized as acute and chronic The acute condition is known as mountain sickness It appears during or soon after ascent and lasts from a day or two to a week The chronic condition includes symptoms that persist, to some extent throughout the sojourn at the high altitude

The acute disturbance or mountain sickness may develop rapidly or slowly The rapid form breaks out suddenly on entrance into the rarefied air It is characterized by a rapid pulse nausea vomiting physical prostration which may even incapacitate one for movement livid color of the skin buzzing in the ears dimmed sight and fainting fits

The slow form of mountain sickness is the more common With it the newcomer at first complains of no symptoms In fact he frequently is somewhat exhilarated Occasionally he finds that in stooping over and raising up again he becomes dizzy and that slight exertion makes him breathless Even at this time examination reveals blueness of the lips edges of the eyelids gums and under the finger nails Some hours later he begins to feel ' good for nothing and is disinclined to exert himself because of a feeling of weakness and exhaustion Soon a slight headache which is usually frontal begins and is likely to grow in severity and to become distressing during the night Along with the headache comes nausea and often vomiting Abdominal pain and diarrhoea often occur

that early in the experiment the field of vision narrowed He attempted to read but found it difficult to do so He seemed unable to get the meaning of what he read and reread almost every paragraph He experienced effort in focusing the eyes on the print Later palpitation of the heart headache and abdominal pains occurred The experiment was discontinued because of increasing discomfort After the experiment the headache was very severe he was pale suffered from nausea and vomiting and was unable to eat supper

Major Westover after his successful flight in the National Balloon Race held at Milwaukee reported that during the first part of the flight he and his aide felt no physical effects other than stimulation About midnight both felt a little distressed and found it difficult to breathe normally About 6 A M at which time they were at an altitude of 15 000 feet he was further annoyed by palpitation of the heart serious belching and a noticeable lack of energy A little later he began to vomit and continued to do so at intervals during the next $3\frac{1}{2}$ hours

Chronic Disturbances at High Altitudes

The untoward symptoms experienced after acclimatization are as a rule not outspoken One questions whether any of them occur at altitudes of less than 10 000 feet and only find them clearly developed at altitudes of 13 000 or 14 000 feet and higher

There is a popular belief among those who live above 5 000 feet that high altitudes are hard on the nervous system Moleen [1] finds that altitude does not cause a definite syndrome but rather a state or condition of the nervous system probably best characterized as an irritability or hyperexcitability which may manifest itself in the motor sensory or psychic spheres or in a combination of them in an otherwise normal individual The patients complain of a mental unrest approaching anxiety and a failure to concentrate or sustain the attention There is increased rapidity of developing fatigue with a feeling of muscular weakness and diminished physical endurance

Such nervous conditions at moderate altitudes say up to 10 000 feet may be regarded as evidence of inadequate acclimatization Sewall [2] regards anemia as a dominant constitutional disorder of high altitudes Normally the number of red corpuscles and the total content of hemoglobin of the blood should be increased at high altitudes Often this does not occur and the failure to make this compensation is responsible for the type of anemia here referred to Moleen believes that the nervous symptoms disappear when the blood forming centers are stimulated If this is true then the above mentioned nervous conditions may be regarded as chronic manifestations of altitude disturbance

Ravenhill [7] is of the opinion that acclimatization does not render one less liable to the effects of fatigue at high altitude He wrote My experience and that of most of my fellow residents was that the longer a man lived at a height of 15 400 feet the less capable he became of resisting fatigue there

Susceptibility to Mountain Sickness

There seems to be no type of individual of whom one can say that he or she will or will not suffer from mountain sickness at a certain altitude Women and children are less susceptible to an attack than men, but young strong and healthy persons may be prostrated The time of onset, severity, and duration of an attack so far have not been predictable

Mining companies, that work properties at altitudes of 13 000 to 16 000 feet require new candidates for employment at and in those mines to pass a rigid physical examination In spite of this, it frequently happens that men in seemingly perfect health are unable to live at such altitudes and the company is obliged to incur unnecessary expense in securing the required number of workers

The most hopeful suggestion of a test for susceptibility that has yet been made is that of Harrop[18] who during the Anglo-American expedition to the Andes mountains in Peru determined the diffusion constant of the lungs for the members of that expedition The diffusion constant is defined as the number of cubic centimeters of oxygen which will diffuse from the alveoli of the lungs into the blood in one minute at a pressure difference of one millimeter He found that the severity of the symptoms of mountain sickness, exhibited by the eight members of the party were in direct proportion to the value obtained for their diffusion constants Those having a value over 40, when at 14 300 feet, suffered very little or not at all while those with one of 30 to 25 had severe attacks In adults variations in the diffusion constant range from 23 to 65 If a simple quick method could be devised for this determination it would be of practical value in the prediction of liability to an attack of mountain sickness and should likewise be of value in the field of aviation

Time a Factor in the Development of Mountain Sickness

Surprise is sometimes expressed over the fact that the aviator does not suffer from so called mountain sickness It seems that the reason cases are not reported is that he does not spend sufficient time at high altitudes Experiments conducted in the low pressure chamber at the Aviation School of Medicine prove this to be a fact In the usual type of experiment in which the pressure is lowered to correspond with the ascent of the airplane the subject of experimentation develops typical altitude symptoms such as we have previously described as characteristic in airplane and balloon flights If, however when a low pressure has been attained it is then maintained for several hours typical "mountain sickness symptoms may appear The record of one subject[35] for whom the pressure in the chamber was lowered at a rate comparable to ascending in an airplane 1000 feet per minute to 400 mm, approximately equivalent to an altitude of 17 000 feet and maintained for 3 5 hours, reveals

makes use of exigent and permanent adjustments The exigent adjustments are immediately effective and temporary in nature while the permanent adjustments are slowly developed and are lasting The exigent adjustments disappear quickly when the ordinary atmospheric content of oxygen is restored or a descent is made The permanent adjustments give acclimatization and persist for days or weeks after descent

Both the exigent and the permanent adjustments of acclimatization tend to bring the delivery of oxygen to the tissues up to the need of the organism but they are not necessarily adequate When an ascent is made rapidly by means of a balloon or an airplane the exigent adaptive changes provide more oxygen than would be the case if the body were unresponsive to the decrease in available oxygen but they are not wholly adequate for great heights In some individuals these adjustments are so inadequate or fail altogether that mental inefficiency or circulatory difficulties appear at altitudes of 13 000 and 15 000 feet while in others they maintain the efficiency at an altitude of 20 000 feet or more The altitude limit for consciousness in the unacclimatized man is around 24 000 or 25 000 feet

Even the changes of acclimatization probably fail to provide entirely for the oxygen needs of the organism There is at such altitudes as 14 000 feet a constant deficit often slight in amount but ever present if we may judge by the chronic symptoms of anoxemia shown by the natives in the Andes mountains The adjustments of acclimatization permit man to survive higher altitudes than would be possible if he were to be suddenly transported to them Thus in the balloon flight reported by Tissandier[6] made in 1875 to a height of about 28 000 feet one man fainted and two died while two acclimatized men Colonel Norton and Dr Somervell in the Mount Everest expedition in 1924 endured the strenuous efforts of climbing without an extra oxygen supply to 28 100 feet and slept well during a night spent at 27 000 feet Odell who was a member of the Everest expedition wrote[76] One is so often asked what it feels like living up at these altitudes and the only reply that can be given is that after some degree of acclimatization one's sensations are really quite normal and it is only when great exertion is necessary that one feels like nothing on earth For physical work at such altitudes the changes of acclimatization are very inadequate Yet at such altitudes as 14 000 to 16 000 feet it was observed that the Tibetans ran up steep hillsides chasing and shouting at their animals without being winded

Acclimatization has been found to occur at all altitudes at which men have sojourned Colonel Norton[76] is of the opinion that everybody has a certain limit up to which under favorable circumstances he may become acclimatized This limit he places at between 19 000 and 23 000 feet However it should be noted that his experience was with the robust Some individuals can not live continuously at 10 000 feet

While it is probably true that most of mankind who live at altitudes above 14 000 feet show some symptoms of anoxemia it is questionable whether

The Anglo American Andes expedition[4] found, at altitudes above 14 000 feet a distinct slackening of energy with an unnatural slowness and clumsiness when at work. The desire to do was unimpaired but the capacity was distinctly lessened. It is generally admitted that the same industry and application as shown at sea level cannot be expected and that the best results are obtained by short periods of work interspersed with relatively long rests. Norton[5] in his account of the 1924 expedition to Mount Everest, speaks of the very serious malaise experienced at 16 000 feet. Walking is a labour and in the keenest air there is no exhilaration rather is there an indefinable feeling of discomfort and distress. He further writes "yet I am convinced that life above 16 000 feet is never quite what it is below that level. There seems to be something lacking all the time and indeed there is something lacking and that something the very breath of life oxygen."

The lack of oxygen accounts for the chronic cyanosis sometimes seen at altitudes above 1 000 feet. The Anglo American expedition to the Andes[4] found cyanosis constantly in all faces of natives at 14 000 feet who showed any blood color. Barcroft[5] writes "Many of them were very sallow and ill looking having rather yellow skins unrelieved by any colour conferred by the blood but where there was a flush it was of a plum colour."

An outstanding chronic effect of altitude is breathlessness during physical exertion. When one is at rest the breathing may be as comfortable as at sea level but even at 14 000 feet exercise may greatly augment it. The Everest expedition[6] found this noticeable at 14 000 feet while above 19 000 feet the slightest exertion made breathing labored and difficult. The dyspnea of exertion may lessen with acclimatization but at great heights it will never wholly disappear.

Clubbing of the fingers is often associated with chronic oxygen want in pulmonary and cardiac lesions. The Anglo American Andes expedition found that this condition frequently occurred in moderate degree among the natives in the Andes.

Loss of weight is common among dwellers at high altitudes. Some individuals lose rapidly during the first part of their sojourn and later regain a part of the loss. The appetite wanes and is capricious, probably this is the cause of the loss in weight. It is generally thought that the sleep is disturbed and of shorter duration than normally. The Everest expeditions however showed great individual variations. Somervell slept well at 25 000 feet and Norton slept well and had an excellent night at 27 000 feet.

The Variety of Adaptive Response to High Altitudes

The human organism does not remain passive when its oxygen supply becomes deficient. It immediately begins to alter the activity of those of its mechanisms which have a part in securing and delivering oxygen so that there may be an increased supply of this vital necessity to the tissues. The body

feet the amount of oxygen that leaves the blood per second must be very materially reduced Then there is an added difficulty in that a chemical change in the blood causes the hemoglobin to hold on to the oxygen more tightly than it ordinarily does at sea level

Individual differences in the effectiveness of the respiratory compensation as revealed by the alveolar air composition show well why some men tolerate a given high altitude better than others We found that in several flights to 15,000 feet one man had an average alveolar oxygen pressure of 54 mm while another had only 43 mm

There occur during flights changes in the blood which affect its acid base balance and its content of hemoglobin and red corpuscles The deficiency of oxygen by stimulating the respiratory center of the brain and thus increasing the breathing causes an increased amount of carbon dioxide to be blown off from the arterial blood Since the hydrogen ion content of the blood is determined by the proportion of carbonic acid to bicarbonates it follows that the blowing off of carbon dioxide that occurs with the augmented breathing disturbs this proportion and causes an increase in the alkalinity of the blood that is the bicarbonates of the blood preponderate more than normally over the carbonic acid This gives the condition known as alkalosis and it is this increase in alkalinity that causes the hemoglobin to hold on more tightly to oxygen In a majority of mankind some degree of alkalosis of the blood must be present during all airplane flights to heights above 4 000 to 8 000 feet at which altitudes the breathing is ordinarily augmented

An increase in the blood content of hemoglobin and red corpuscles is sometimes experienced during flights but individuals vary greatly in their ability to secure this change By experiments in a low pressure chamber it was shown that when men are held for awhile at oxygen pressures comparable to those of altitudes of from 15 000 to 0 000 feet an increase in both the erythrocytes and hemoglobin occurs in approximately 80 per cent of all cases The erythrocyte increase ranged between 4 and 20 per cent and that of hemoglobin between 3 and 10 per cent The increase was found in the venous as well as capillary blood The majority of men do not show the change in less than from 40 to 60 minutes but about 10 per cent develop it within 25 minutes

When the erythrocytes and hemoglobin begin to show an increase the man gives evidence of improvement in his general condition his color improves he becomes more alert and the pulse frequency retards

The gain to the tissues from the increase in erythrocytes and hemoglobin is that a unit volume of blood can carry for a given oxygen pressure more oxygen than it would without this change Furthermore as Barcroft has shown because of this change the blood leaves the capillaries less depleted of oxygen and with its oxygen pressure slightly greater than it would be otherwise This means that the average pressure of the oxygen going to the tissues is also higher than it might have been a condition that favors the use of oxygen in metabolism

there is a measurable degree of anoxemia in the acclimatized at altitudes under 10 000 feet Our observations in the Pikes Peak region have failed to reveal in people who resided up to a height of 10,000 feet, any clear limitations in the accomplishment of physical work

The Mount Everest expeditions showed that men who have once experienced high altitudes will acclimatize more rapidly than those who ascend for the first time It was also found that the rate at which one acclimatizes does not determine one s effectiveness Odell acclimatized slowly and yet in the end appeared to be the most fit member of the expedition when at the highest altitudes

Physiological Responses to Altitudes Experienced by the Aviator

As the aviator ascends changes occur in the breathing in the morphological and chemical composition of the blood in the action of the heart and in the circulation of the blood Those of the respiration and the blood provide for a more adequate supply of oxygen to the tissues, while those of the circulatory system are probably expressions of mal adjustment

The adaptive breathing response begins [9, 23] in some aviators as low as 3 000 or 4 000 feet but in the majority not until an altitude of 8 000 feet is reached The quantity of air respired is gradually increased but the total increase per minute over the volume breathed at sea level does not average much more than five liters in men flying at an altitude of about 28 000 feet [37] The fainting type of reactor averages an increase of only 3 5 liters for this altitude Most men show merely an increase in the depth of breathing without a change in the frequency A small number may experience an increased frequency of breathing while even a still smaller number have a reduction in the frequency The essential feature of the respiratory compensation is that more air at each breath gets past the dead space of the lungs and thus raises the alveolar oxygen pressure more than would be the case with shallow breathing

In spite of the increase in breathing there is a steady fall in the alveolar oxygen pressure of the lungs during an airplane ascent Schneider and Clarke [37] found that the alveolar oxygen pressure fell from an average of 100 5 mm at sea level to 49 8 mm at an altitude of 15 000 feet This means that at sea level the blood is normally 96 per cent saturated while in flying at an altitude of 15 000 feet it is only 82 per cent saturated with oxygen When this difference is visualized from the standpoint of pressure rather than the extent to which the blood is saturated it is clearly evident why there is marked anoxemia in the body The rate at which oxygen flows from the blood to the tissues is determined not by the amount of oxygen in the blood but by the pressure of the oxygen At sea level the pressure of the oxygen in the blood as it arrives at the capillaries is approximately 95 mm while in the aviator at 15 000 feet it is only about 45 mm With 50 mm less driving or delivery power at 15 000

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There occur during flights changes in the blood which affect its acid base balance and its content of hemoglobin and red corpuscles The deficiency of oxygen by stimulating the respiratory center of the brain and thus increasing the breathing causes an increased amount of carbon dioxide to be blown off from the arterial blood Since the hydrogen ion content of the blood is determined by the proportion of carbonic acid to bicarbonates it follows that the blowing off of carbon dioxide that occurs with the augmented breathing disturbs this proportion and causes an increase in the alkalinity of the blood that is the bicarbonates of the blood preponderate more than normally over the carbonic acid This gives the condition known as alkalosis and it is this increase in alkalinity that causes the hemoglobin to hold on more tightly to oxygen In a majority of mankind some degree of alkalosis of the blood must be present during all airplane flights to heights above 4 000 to 8 000 feet at which altitudes the breathing is ordinarily augmented

An increase in the blood content of hemoglobin and red corpuscles is sometimes experienced during flights but individual vary greatly in their ability to secure this change By experiments in a low pressure chamber it was shown that, when men are held for awhile at oxygen pressures comparable to those of altitudes of from 15 000 to 20 000 feet an increase in both the erythrocytes and hemoglobin occurs in approximately 80 per cent of all cases The erythrocyte increase ranged between 4 and 20 per cent and that of hemoglobin between 3 and 10 per cent The increase was found in the venous as well as capillary blood The majority of men do not show the change in less than from 40 to 60 minutes but about 10 per cent develop it within 5 minutes

When the erythrocytes and hemoglobin begin to show an increase the man gives evidence of improvement in his general condition his color improves he becomes more alert, and the pulse frequency retards

The gain to the tissues from the increase in erythrocytes and hemoglobin is that a unit volume of blood can carry for a given oxygen pressure more oxygen than it would without this change Furthermore as Barcroft[a] has shown because of this change the blood leaves the capillaries less depleted of oxygen and with its oxygen pressure slightly greater than it would be otherwise This means that the average pressure of the oxygen going to the tissues is also higher than it might have been a condition that favors the use of oxygen in metabolism

With regard to the circulatory changes that occur during a progressive anoxemia such as is experienced during an airplane flight to a very high altitude there is at present some difference of opinion as to how the available data should be interpreted Some believe that the rate of blood flow is increased and others that, when the anoxemia becomes great, the blood tends to pool in the abdomen The readily observed conditions in the circulatory mechanism are as follows The frequency of the heart beat augments The acceleration is at first slight beginning at an oxygen pressure comparable to an altitude of 4 000 feet The pulse gradually increases up to an oxygen pressure comparable to altitudes of from 13,000 to 18,000 feet After this the acceleration is much more rapid [3]

The systolic blood pressure at first is maintained or gradually rises, while the diastolic pressure undergoes a similar change or gradually falls Under extreme anoxemia both of these pressures may fall and typical syncope result [7] Almost without exception the venous blood pressure gradually falls The hand volume and the blood flow through the hand, as determined by Stewart's calorimeter, show a falling off, when the anoxemia becomes severe Apparently the tone of the peripheral blood vessels is not decreased as might be expected but rather increased with the result that the rate of flow of blood through the capillaries is retarded Associated with the peripheral vasoconstriction and the diverting of blood to the interior of the body is the fall in venous blood pressure This seems to be due to a pooling of the blood in the splanchnic vessels That splanchnic dilatation with pooling occurs seems evident from the fact that abdominal compression prevents in large part the fall in venous pressure [35]

Sands and DeGraff [*], from studies on dogs of the phenomena of circulation in anoxemia find indications that the circulation improves up to oxygen pressures comparable to an altitude of 22 000 feet and that this helps to supply the tissues with normal volumes of oxygen

The Physiological Changes of Acclimatization to Altitude

In acclimatization the breathing is permanently augmented the concentration of the blood in hemoglobin and erythrocytes is increased, the total amount of hemoglobin and erythrocytes is also decidedly increased the blood plasma is altered in its composition the erythrocytes are increased in alkalinity, and the blood forming bone marrow becomes more abundant All these changes have a part to play in the problem of oxygen supply As Haldane [16] has pointed out the organism in acclimatization is in a physiologically different state from what it was before exposure to the low barometric pressure of the high altitude

The first clearly recognized compensation to altitude in a passive ascent of a mountain by automobile or railway train is found in the breathing The breaths may deepen slightly during the ascent so that by the time the destination is reached the minute volume is somewhat increased However the process of augmentation of breathing is then by no means completed The Pikes Peak

expedition[3] demonstrated that it requires from 3 to 19 days for the process to be completed. Alveolar air analyses reveal an important gain to the body during this period, which is illustrated by the following typical response. One subject had an alveolar oxygen pressure of 42.7 mm. 4 hours after arrival on the summit, while on the 17th day it had risen to 55.6 mm. Residence at a high altitude during the period of growth produces a larger chest than is normal for inhabitants at sea level. The Andes expedition[4] found the breadth of the chests of the native Indians about 10 per cent greater than of men of their height from low altitudes.

The gradual increase in the breathing that takes place during the first days of residence at the high altitude is associated with changes in the composition of the blood plasma. Y. Henderson and Haggard[1, 19] set forth the events of the hemato-respiratory changes of acclimatization as follows: (1) there is a lowering of the oxygen tension of the inspired air; (2) the respiratory center of the brain is stimulated; (3) this causes excessive breathing with a blowing off of CO_2; (4) this results in a decrease in the ratio of $H_2CO_3 : NaHCO_3$, which means a lowering of the hydrogen ions, an alkalosis of the blood plasma; and (5) there follows this a compensatory elimination of alkali from the blood.

Haldane explains these hemato-respiratory changes of acclimatization as follows. The hydrogen ion concentration of the blood is regulated with great delicacy by the respiration on the one hand and the kidneys and liver on the other, the respiration doing the rough and immediate work by increasing or decreasing the elimination of carbon dioxide and the kidneys the finer and slower work by adjusting fixed acid and alkalies. Oxygen want serves as an additional stimulus to the respiratory center, causing an increased amount of carbon dioxide to be blown off from the arterial blood. This loss of carbon dioxide makes the blood abnormally alkaline and causes the kidneys and liver to slowly redress the balance, the kidneys by excreting the excess of alkali and the liver by forming less ammonia. The increase in breathing during the process of acclimatization is the result of the gradual adjustment of the alkalosis of the blood plasma. As the alkalosis becomes compensated the full effect of oxygen want on the breathing is more and more unmasked. Normally alkalosis reduces the minute volume of breathing. Henderson has shown that the breathing under ordinary circumstances varies inversely with the bicarbonate content of the blood. The total bicarbonate content of the blood is clearly reduced in the acclimatized person, and by as much as it is reduced below the sea level normal by that proportion is the respiration increased at the high altitude.

The members of the Andes expedition attempted to determine the hydrogen ion content of the blood in acclimatized persons but were not satisfied that their results were decisive. They conclude,[4] however, that the blood is not more acid at high altitudes than at sea level. Whether it is slightly more alkaline they were unable to determine. Haldane[16] believes a very slight degree of alkalosis remains even in acclimatization. Even if this is true it is evident that in acclimatization the alkaline reserve of the blood is reduced

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Another factor that favorably influences the oxygen-carrying capacity of the blood is a chemical change in the interior of the red corpuscles. This was first pointed out by the Andes expedition [4] and later explained by Barcroft. As the blood plasma undergoes its chemical changes some of the chlorine passes out from the erythrocytes leaving behind potassium which makes their interior more alkaline. This increases the affinity of hemoglobin for oxygen and permits the blood during its passage through the lungs to take up oxygen more rapidly. Hence in the acclimatized person oxygen passes into the blood more rapidly and the blood will probably leave the lungs somewhat more nearly saturated with oxygen.

Circulatory Reactions During Period of Acclimatization

The pulse frequency is accelerated on going into the mountains to altitudes above 10 000 feet. It is generally recognized that at altitudes up to 8 000 or even 9 000 feet, acclimatized persons do not show this acceleration. On taking up residence at higher altitudes one who becomes mountain sick will experience a marked acceleration the first day and a retardation upon recovery. Those who remain well are likely to show in the basal pulse rate, i e the pulse rate while still in bed in the morning, an increase of a few beats each morning for from three to four days [29]. Then follows a period of maintained high rate after which there is a slow retardation which eventually brings the rate back to or near normal. The amount of acceleration will depend upon the physical condition of the men. There will be less in the individual who is in the pink of condition and more in the sedentary worker who is physically below par.

Physical exertion accelerates the pulse more at high than at low altitudes. This effect is very pronounced during the first days of residence and is less as acclimatization progresses [31]. But even in the acclimatized an abnormal degree of acceleration occurs in work.

The arterial blood pressure, systolic and diastolic, is ordinarily unaffected by altitude or shows a slight fall. The latest evidence for this statement appears in the report of the 1924 Everest expedition. But during an attack of mountain sickness both the systolic and diastolic pressures rise and may continue high for several days thereafter.

Physical exertion causes the arterial pressure to rise inordinately during the first days of residence but after acclimatization moderate exertion causes little more rise, if any, than the same work does at sea level [31]. However in more strenuous work the pressure still rises abnormally high. The more perfect acclimatization the less is the altitude disturbance of the pulse and blood pressure during exercise. An unusually rapid heart and a high arterial blood pressure may well be taken as evidence of poor compensation to the altitude. The striking feature about the circulatory reactions to altitude is that they become steadily less pronounced as acclimatization proceeds.

Contrary to common belief the Andes expedition found the heart smaller

appreciably below sea level normal The net result however, of the acclimatory process is that the normal ratio of H_2CO_3 $NaHCO_3$ is practically restored but with a reduction in the body of the total quantity of each of these compounds H_2CO_3 and $NaHCO_3$

Once the blood alkali has been reduced and the hydrogen ion content of the blood restored to normal then the breathing is fixed at its new level If then a descent is made to a low altitude the breathing will continue as voluminous as at the high altitude It will gradually be reduced during a period of days or weeks, but the rate of reduction will be determined by the time required for the blood to regain its normal sea level content of alkali

The morphological changes of the blood in acclimatization include a permanent increase in the number of red corpuscles and platelets and in the proportion of lymphocytes to polynuclears in the white cell count The red cells (erythrocytes) increase rapidly during the first three or four days of residence at the high altitude and then more slowly for a period of several weeks The first increase has been accounted for by the use of several phenomena by a temporary loss of fluid from the blood[8], by the advent into the blood of a mass of corpuscles from some store house where an excess is available for emergency[30], and by an increased manufacture of erythrocytes by the red marrow of the bones Barcroft[5] believes that the spleen may add 100 cubic centimeters of corpuscles to the circulation or about 5 per cent of the whole number in circulation

The evidence for a new formation of erythrocytes is now completely convincing in character Under the stimulus of a chronic lack of oxygen the amount of red marrow is increased in the bones As it grows the daily production of new corpuscles also gradually increases This phenomenon continues until not only the percentage content of the blood in hemoglobin and erythrocytes is above normal but until the total quantity of these is much greater in the body

Miss Fitzgerald[10] finds that among people living at high altitudes the hemoglobin content of the blood is larger than the sea level normal of 100 per cent by about 10 per cent for every 100 mm that the barometric pressure is less than at sea level (760 mm) This means that the oxygen capacity of the blood of acclimatized inhabitants of a high altitude is greater by that proportion Thus if 100 cubic centimeters of blood at sea level carry 18 5 c c of oxygen at 20 000 feet where the barometric pressure is 360 mm it can carry as much as 26 cubic centimeters or 40 per cent more than at sea level

This change of acclimatization means that the store of dissociable oxygen in the blood is larger at the high altitude than it otherwise would be and that with a given flow of oxygen into the tissues the pressure of oxygen will not fall as low as though the hemoglobin had not increased Any slight increase in oxygen pressure must be advantageous to the tissues and lead to an increased efficiency in their function

The Treatment of Altitude Disturbances

Persons who ascend gradually to great heights taking days or weeks to reach the desired altitude will probably never experience mountain sickness or any of the other more formidable effects of altitude There is no panacea for mountain sickness If one desires to live in high altitudes he must undergo the adjustments of acclimatization So if he ascends too rapidly for the slow accomplishment of these adjustments there must necessarily be a period of physical discomfort the severity of which will vary with the individual

The breathing of oxygen will prevent or alleviate the symptoms of mountain sickness A press representative who came to interview the members of the Anglo-American Pikes Peak Expedition [8] became so alarmingly blue and faint that we gave him oxygen which revived him at once and immediately restored his color and spirits He continued all right for a few minutes and then again became blue and faint and was again completely revived by the oxygen While oxygen will afford temporary relief it is believed that this would only postpone the acclimatizing action and that eventually one would be compelled to submit to nature s course of treatment An extra supply of oxygen does maintain normal physical and mental activity in the extreme altitudes attained in aviation

Fatigue and a poor physical condition favor the development of mountain sickness Hence a period of physical training before making an ascent in the mountains will increase the power of resistance to the malady Wherever feasible the ascent should be by railway or automobile

Ravenhill [27] found that the treatment of the normal type of mountain sickness resolved itself into rest in bed with the windows well open and a day or so of quiet after all symptoms had disappeared He found that aspirin invariably relieves the headache while phenacetin is not so effective probably because of its depressing effect on the heart A light diet is prescribed for the first few days of the sojourn at the altitude and the bowels are kept active but in no case is a purge desirable He says that in bad cases including those that develop cardiac and nervous symptoms the conditions must be treated as they arise and that the patient must be sent down as soon as possible

Contraindications to Going to High Altitudes

It is doubtful whether we have any satisfactory evidence that moderate altitudes have proved injurious to mankind It is generally assumed that it is dangerous to send patients with any form of heart disease to a high altitude but experience does not bear this out Hall [17] Schrumpf [35] Zederbaum [42] and Wyss [41] disagree with this opinion and find altitudes up to from 5 000 to 7 000 feet beneficial in a number of diseases of the heart and blood vessels

at the high than low altitudes. However, as the result of the strenuous climbing the members of the Everest expedition showed signs of dilatation of the heart for some time after descent; in two it was decidedly marked.

The Seat of Action of Anoxemia in Altitude Disturbances

While it is generally admitted that a lack of oxygen causes the altitude disturbances experienced by the body, it is probable that a complete explanation has not yet been given.

Experiments in a low pressure chamber and with anoxemia produced by the rebreathing method indicate that the brain is the most sensitive part of the body to a deficiency of oxygen. As has already been pointed out for the rapidly developed anoxemia such as is experienced in an airplane flight, inefficiency is either caused by the depressing action of oxygen starvation on the forebrain as is the case with the non fainting type of reactor, or on the hindbrain especially the medulla oblongata when fainting occurs. The serious consequences of anoxemia are certainly ushered in by symptoms originating with the central nervous system.

With regard to mountain sickness Barcroft[5] has said: In the last resort the symptoms of mountain sickness are less due to deficient oxygen supply to the body as a whole than to deficient oxygen supply to the brain. There is much about mountain sickness that reminds us of seasickness. Both it seems are due to abnormal conditions which disturb brain centers. In mountain sickness the medulla is most disturbed. Some of the factors that seem to cause mountain sickness are clearly seen to be only contributing factors when the above explanation is accepted. Thus physical exertion and the ingestion of alcohol or food precipitate the attack by diverting blood from the medulla, thus depriving it of oxygen still more.

Whether oxygen deficiency acts directly or indirectly on the medulla can not as yet be settled. Barcroft[3] in his earlier writings was of the opinion that the vomiting center in the medulla is stimulated by a lack of acid in the blood. Haldane, Kellas and Kennaway[1] and Sundstroem[40] held that at least a secondary cause is an abnormally large proportion of alkali in the blood. With regard to either of these possibilities we[33] showed by an analysis of the alveolar air changes of men during a sojourn on mountains that the symptoms of mountain sickness frequently occurred at a time when the hydrogen ion content and total content of acids and bases in the blood had not as yet altered. It is probable that the deficiency of oxygen acts within the brain itself to prevent the normal sequence of cellular metabolism.[20] The supply of oxygen determines the amounts of lactic acid and carbon dioxide formed in the tissues. Diminished oxidation in the medulla leads to an increased production and accumulation of these within the nerve cells and thus modifies their function.[1]

The increase in the amount of hematopoietic tissue of the body is probably a direct response of bone marrow to oxygen deficiency which acts as a stimulus to hyperplasia.

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High altitudes ought to be avoided by persons whose power of compensation is below par, as may be the case in severe anemia and pulmonary emphysema Schrumpf believes that the mountains are directly contraindicated n uncompensated valvular heart lesions and in coronary sclerosis Wyss finds that high altitudes are not suited to persons with nephritis and arrhythmia He also finds against cases of marked dyspnea, cardiac dilatation, and blood stasis He believes it is imperative to have all cardiac patients keep absolutely quiet for everal days after they reach the high altitude

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CHAPTER XIX – C1

DECOMPRESSION SICKNESS (CAISSON DISEASE, COMPRESSED AIR ILLNESS BENDS AERO EMBOLISM)

By ALBERT R. BEHNKE

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usually are decompressed in contrast with the rapid decompression frequently applied to lower animals characteristic manifestations of pain (bends) asphyxia (chokes) and paralysis can be attributed to intravascular bubbles The formulation of a treatment procedure for decompression sickness and the employment of helium oxygen mixtures as a substitute for air are especially valuable contributions by the U S Navy

PRIMARY PRESSURE PHENOMENA

Effects of Compression Applied Equally to All Parts of the Body — The body has been compressed to almost 18 atmospheres equivalent to a diving depth of 550 feet without demonstrable physiological change attributable to the compression itself provided air has free access to all surfaces of the body e g the membranous linings of the middle ear frontal sinuses and ethmoid and mastoid air cells Although the *absolute* cerebrospinal fluid and blood pressures may be increased by 18 atmospheres the *relative* pressure readings may not be altered by as much as 1 mm Hg Insofar as the pressure force operates the brain is not in a closed box but is subject to the same compressive force as is the skin That considerable pressure in fact up to hundreds of atmospheres is well tolerated by protoplasm has been shown by McKeen Cattell[1] Similarly a decrease in ambient air pressure equivalent to an altitude of 50 000 feet will not in itself cause injury although metabolic changes attributed to low pressure have been reported by Cool This tolerance implies equal distribution of pressure to preserve unaltered the structure of tissues and the body as a whole

Effect of Unequal Pressure Application —If the pressure is not equally distributed over all body surfaces a pressure difference between tissues and the ambient atmosphere of less than 50 mm Hg (1 psi) will alter the shape of tissue and induce congestion edema hemorrhage and pain

The effect of a compression and a difference in pressure acting on the body is observed in a pearl diver subjected to an additional compressive force of one atmosphere for every 33 feet of descent At a depth of 100 feet for example the total pressure acting on his body is of the order of 4 atmospheres The air in the diver s chest at the surface (let us say 6 000 cc) is compressed at this depth to one fourth of the initial volume or 1 500 cc (residual air volume) Should the diver descend deeper hydrostatic pressure cannot compress the rib cage to a

Introduction

It has long been known that too rapid decompression of divers and compressed air workers gives rise to the formation of bubbles in the blood stream and fatty tissues and to symptoms if the bubbles are sufficiently numerous and are located in critical areas. The numerous studies sponsored by the Army and the Navy relative to the physiological effects arising from the rapid decompression of aviators have added extensive and valuable quantitative data relative to the influence of exercise, age, degree of obesity, and diurnal and environmental conditions on the incidence of symptoms. Procedures have been validated for the selection of individuals relatively resistant to decompression sickness. Principles underlying formation and growth of bubbles have evolved from meticulous experiments. Histological studies have shown precisely the location of bubbles and a new finding presented, the watery vacuoles in liver cells following too rapid decompression. It is emphasized that symptoms are similar irrespective of the pressure level prior to decompression, i.e., ascent from diving depths or ascent to high altitudes.

Despite these studies it has not been possible to demonstrate the manner in which intravascular bubbles produce symptoms although ischemia, distension of the vascular wall and other possible mechanisms have been analyzed. Nor is the relation of extravascular bubbles to symptomatology certain. On the other hand, from studies of diving and caisson decompression sickness beginning with the fundamental investigations of Paul Bert, Heller, Mager, Von Schrotter and Boycott, Damant and Haldane, there is good evidence that under conditions in which men

submarine escape training tanks from depths of 100 feet and ocasionally in the open sea from depths of 200 feet

During such ascents the compresed gas in the lungs and in the breathing bag escapes through a relief flutter valve located on the bottom of the breathing appliance In this manner the intrapulmonic pressure closely approximates ambient hydrostatic pressure

If the individual, instead of breathing freely holds his breath and ascends to the surface the intrapulmonic pressure becomes higher than the hydrostatic pressure and the difference in pressure of the order of 80 mm Hg[2] overdistends the lungs ruptures the alveolar sacs and blood vessels and gas may be forced or aspirated into the blood stream The gas emboli subsequently produce symptoms referable to the central nervous system and the circulation

In pressurized aircraft the possibility of sudden loss of pressure creates the hazard of explosive decompression involving expansion of abdominal gases overdistension of the lungs and even boiling of the blood and body fluids at body temperature It has been found by German investigators that explosive decompression irrespective of rate and magnitude does not produce injury of the lungs when the glottis is open With the glottis closed intrapulmonic pressures of the order of 80 mm Hg can overdistend the lungs and produce the type of air embolism seen in submarine escape experiments with the Momsen lung The fundamental requisite to the production of pulmonary injury is the building up of intrapulmonic pressure to a level (about 50 to 80 mm Hg) where alveolar vessels rupture and air is aspirated into the circulation during succeeding respirations Protection against rapid gas expansion or boiling of the blood can be afforded by suitable application of counter pressure to prevent the increase in volume of the body

Spontaneous Pneumothorax—Either with or without air embolism during rapid decompression spontaneous pneumothorax may occur in the distended lung The mechanism of this type of injury has been outlined by Gersh[4]

Overdistension of Abdominal Viscera—In ascent from deep diving depths the expansion of gas swallowed under pressure in the stomach and segments of the large bowel is a serious restraint to further decompression A viscus once having been distended with gas appears to lose much of its motility In distension of the stomach for example the cardiac and pyloric sphincters remain contracted and prevent immediate elimination of gas

volume much less than that occupied normally by residual air. Thus a condition known as a "squeeze" is produced. The effect of the "squeeze" is to force blood and tissue fluid into the respiratory passages where the residual pulmonary air tends to be under less pressure than the pulmonary membranes and rib cage which are under the ambient hydrostatic pressure.

Effect of Pressure Differences on Ears, Sinuses and Teeth.—In a similar manner aural and sinal membranes are injured by a "squeeze", if the corresponding ostia of the lined spaces do not permit the free ingress of air and consequent equalization of pressure.

During the past 12 years thousands of American submarine personnel have been subjected to 50 psi gage pressure in naval recompression chambers in connection with the submarine escape drill. From 5 to [illegible] per cent of the trainees at any given time have been able to accommodate readily the excess pressure chiefly because of varying degrees of infection of the upper part of the respiratory tract (colds), producing edema of lymphoid and other tissue to seal the openings of the auditory tubes and less frequently the sinal meatuses.

In aviation during descent from altitude the increased pressure similarly affects individuals to create a condition termed "aero otitis media" by Armstrong and Heim. The prevalence of obstruction of the auditory tubes in apparently healthy individuals is indicated by an incidence of about 10 per cent failure at any given time to accommodate rapidly to pressure changes. About 1 5 per cent of individuals experience sinal pain, and another 1 5 per cent are subject to pain in one or more teeth.

Following acute trauma the audiogram reflects diminished perception of sound over the whole frequency range. As the pathological disturbance undergoes resolution, however, hearing returns to the initial level of acuity. The rarity or absence of proved cases of deafness arising from injury incident to pressure trauma stands in contrast to the permanent aural damage caused by gunfire. Complications of suppurative otitis media, moreover, are infrequent, if the traumatized tissues do not come in contact with water. The spread of infection from the nasopharynx by air passing into the auditory tubes during compression is not established.

Overdistension of the Lungs (Traumatic Air Embolism).—To escape from a sunken submarine an individual may breathe compressed air or oxygen by means of a rebreathing bag such as the Momsen lung. The speed of his ascent can be regulated by a buoy line previously released from the submarine. In this manner ascents have been made routinely in

and 100 per cent oxygen appears to be toxic (substernal distress nose and throat irritation) after a period of inhalation of about 1 hours[13 14] No sharp limit can be set however since individual variation in response is large particularly when physiological variables are not controlled

At a pressure of three atmospheres absolute pure oxygen can be inhaled by most individuals at rest for a period of about three hours Symptoms indicative of pulmonary irritation do not arise but during the fourth hour of inhalation there may occur a rise in blood pressure increase in pulse rate and a contraction of the visual fields Pallor may be extreme Periodic waves of nausea constitute the most common subjective symptom of oxygen toxicity In the decompression of divers

TABLE I

Incidence of Symptoms As A Result of Exposure to Inhalation of Oxygen At Increased Pressures

	DRY CHAMBER		UNDERWATER	
DEPTH	REST Open Circuit	WORK Open Circuit	REST Open Circuit	WORK Open Circuit
30 ft				18 hr dives 1 case (6%) 111 minutes
40 ft	3 2 hr dives no symptoms			23 2 hr dives 8 cases (35%) *69 minutes*
50 ft				
60 ft	0 hr dives no symptoms	13 1 hr dives 13 cases (100) 10 minutes	0 2 hr dives 8 cases (40) 6 minutes	
80 ft	48 2 hr dives 37 cases (77%) 50 minutes		67 1 hr dives 67 cases (100) minutes	
100 ft	9 1 hr dives 6 cases (9) *27 minutes*		0 1 hr dives 0 cases (100%) *18 minutes*	

Minutes indicate average time at onset of symptoms Subjects showing no symptoms are not included in determining average time of onset Dr C J Lambertsen s compilation of U S Navy data)

Secondary Pressure Phenomena Induced by Increased Gas Pressures

Narcotic Action of Nitrogen.—The phenomena previously described have arisen primarily from differences in pressure which have acted to distend and rupture blood vessels and membranes. On a wholly different basis are those presure phenomena associated with disturbances in gaseous equilibria.

When the air pressure is raised to 4 atmospheres or higher, the gaseous nitrogen induces a narcotic action manifest by decreased ability to work and changes in mood, frequently euphoria. A slowing up of mental activity and fixation of ideas are observed. Recollection requires greater effort, and concentration is difficult. Frequent errors may be made in arithmetical calculation and in the recording of data. Motor performance is impaired. The responses are, in fact, similar to those associated with anoxia or alcoholic intoxication. Although all individuals are to some extent narcotized at deep diving depths, stable individuals apparently react to the stress by increased effort and carry out their tasks until consciousness is lost. The unstable individual, on the other hand, is incapable of purposeful effort[5, 6].

Effect of Helium.—The substitution of helium, which has a lower oil water solubility ratio than nitrogen[7], diminishes the narcotic effect of high air pressures. In a simulated dive to 550 feet, in which helium-oxygen mixtures were breathed, the diver remained in good condition throughout and subsequent to the period of the dive[8]. In an air atmosphere divers may lose consciousness at depths of about 350 feet[9].

Case and J. B. S. Haldane[10] have confirmed the finding that air at high pressures (8.6 atmospheres) has an intoxicating effect and that this effect can be abolished by substituting helium or hydrogen for nitrogen.

Effect of High Oxygen Pressure.—The oxygen "black out" or sudden loss of consciousness without dyspnea when high CO_2–O_2 mixtures are breathed during exercise at pressures as low as one atmosphere in contrast with the effect of inhaling AIR–CO_2 mixtures and the confirmation of Campbell's finding[11] that high CO_2 pressures in tissues are associated with high oxygen pressures in the lungs are important recent findings[1]. Even at atmospheric pressure the inhalation of pure oxygen was found by both British and German investigators to be associated with an increase in tissue CO_2 tension. The irritant level for prolonged inhalation of oxygen has been found to be the same for man as for lower animals, namely, about 60 per cent. of one atmosphere (456 mm. Hg),

Despite these limitations oxygen has proved to be of tremendous value in the later stages of decompression and in the treatment of compressed air illness In the administration of oxygen proper humidification and comfortable masks are essential for prolonged inhalation The greatest hazard in oxygen administration in chambers is the danger of fire The proper precautions therefore, must be strictly enforced

Effect of High Carbon Dioxide Pressure —Carbon dioxide enhances the toxicity of oxygen and the narcotic effect of nitrogen In the diver s helmet the percentage of carbon dioxide must be reduced to a minimum During rapid descent in deep sea diving momentary vertigo and confusion are attributable in part to the accumulation of alveolar carbon dioxide as the air pressure rapidly rises in the lungs

With respect to work in compressed air empirical evidence points to a higher incidence of bends in association with a rise in the carbon dioxide level The effective carbon dioxide percentage should not exceed 1 5 per cent although percentages of carbon dioxide up to 5 are fairly well tolerated at normal barometric pressures for periods of at least 60 hours [15]

Symptoms and Signs of Decompression Sickness

The major symptoms or signs of decompression sickness are pain (bends) asphyxia (chokes) and paralysis Minor effects are pruritus rash and fatigue The parts of the body chiefly involved are the extremities (bends) the cardiorespiratory system (chokes) and the spinal cord

Etiology —The primary role of bubbles in producing the symptoms of decompression sickness was indicated long ago by the work of Robert Boyle 1670 Convincing experimental data however, were not available until the investigations of Paul Bert about 1880

There is yet to be determined the mechanism by which intravascular and possibly extravascular bubbles produce symptoms, ischemia vascular distension and local irritation have been considered

Pathological Changes —Permanent lesions attributed to intra or extra vascular bubbles have been found in the spinal cord and in the shafts and epiphyses of long bones

The nervous symptoms according to Heller Mager and von Schrotter[16] are the result of ischemic processes as demonstrated first by Paul Bert in the white substance of the cord Boycott Damant and Haldane[17] however concluded that areas of necrosis in the spinal cord were

(resting state), therefore the pressure for oxygen is limited to two and one half atmospheres If pure oxygen is inhaled during exercise at three atmospheres pressure the tolerance time is greatly reduced Pedaling a bicycle at a rate sufficient to increase normal oxygen consumption three fold limited the safe inhalation of oxygen to a period of about ten minutes at a depth of 60 feet

At a pressure of four atmospheres oxygen usually can be breathed safely by men at rest for a period of fifteen minutes Beyond this period convulsive seizures or syncope may occur While the nervous manifestations of oxygen toxicity are alarming apparently complete recovery follows, when air again is inhaled

Of prime importance is the fact that exercise increases the toxic effect of oxygen It is not surprising therefore that the administration of pure oxygen to divers working in depths exceeding 30 feet has been associated with symptoms of oxygen toxicity In the wet tank symptoms also are more prevalent than in the dry chamber, probably because of increased activity and the attendant accumulation of carbon dioxide in tissues The incidence and classification of symptoms in men at rest and at work during the inhalation of oxygen are shown in Tables I and II

TABLE II

PERCENTAGE FREQUENCY OF VARIOUS SYMPTOMS OF OXYGEN POISONING

	Dry Rest (2)	Wet Rest (5)	Wet Work (5)
No of exposures terminated by symptoms	168	388	1 0
Nausea	57	8 3	17 5
Vertigo	57	8 8	20 8
Twitching	21	63 8	50 0
Anxiety	6		
Paraesthesia	6	4	
Convulsions	4	9 2	68
Respiratory disturbances			
Visual disturbances	6	1 0	
Sensations of abnormality		3	
Tinnitus		6	

(Dr C J Lambertsen s compilation of U S Navy data)

Sludge formation, the close grouping in compact masses of red blood cells separated by zones of clear plasma accompanied the reduction in blood flow This clumping of cells described previously by Swindle[8] is a phenomenon that Knisely has demonstrated under a variety of conditions associated with slowed circulation plasma loss and cell packing

In the studies of Gersh and his collaborators[29 30 31 32 33 34 35] intravascular gas bubbles were found in all tissue and organs of rapidly decompressed guinea pigs but were far more numerous in those rich in fat Extravascular bubbles were observed in tissue rich in fat and in the lipid matter of the adrenal cortex in the myelin sheaths of nerve fibers in bone marrow and in the connective tissue surrounding the tendons of the long muscles

In diving especially following the inhalation of helium oxygen mixtures the upper extremities and shoulders frequently are afflicted with bends Swelling of the arms is not uncommon and crepitus has been elicited along the brachial veins suggesting blockage of venous return as the cause of the edema

Incidence of Symptoms and Signs —Bends occur most frequently followed by skin manifestations vertigo chokes and visual symptoms (Table III)[36 37] Paralysis occurs only occasionally in divers but was reported not infrequently in caisson workers about fifty years ago[18] In the classification of symptoms no attempt is made to define the part of the body primarily injured Thus under brain (Table III) are listed visual disturbances and unconsciousness which may have been caused by cardiorespiratory impairment rather than emboli There is likewise doubt as to whether the sensory disturbances listed under 'spinal cord' arose primarily from spinal cord injury and conversely the etiology of pain designated as bends may be due to a central rather than to a peripheral lesion

Distribution of Pain (Bends) —In caisson workers bends in the lower extremities chiefly the knee predominated In a series of 131 navy dives of comparatively short exposure about 70 per cent of the painful symptoms were in the upper extremities and shoulders In 17 prolonged saturation exposures however bends occurred 5 times more frequently in the lower than in the upper extremities Apart from the apparent influence of duration of the compression period on location of symptoms it has been observed that an exercised part of the body may be more susceptible to bends

Time of Onset of Symptoms —Keays[36] reported that 85 1 per cent of symptoms appeared within one hour after decompression and 14 9

caused by extravascular bubbles This matter of bubble location is of the greatest importance since if bubbles form extravascularly in nervous tissue, every decompression holds the probability of serious consequences With reference to the distribution of areas of injury there is general agreement that the less vascular areas (lower thoracic and lumbar segments) and those high in fat (myelin) content are more often subject to injury

In regard to osseous and arthritic lesions Twynman[18] in 1888 reported bone necrosis in caisson disease and Bornstein and Plate[19] in 1911 reported that chronic arthritis could arise from repeated embolic and nutritional injury following too rapid decompression Plate [1] also reported pathological changes in bone as demonstrated by x-ray That bubbles can be present in marrow or within the cortex of bone is inferred from the pertinent observation that recompression, especially if it is too rapid may intensify the pains of bends This type of pain is believed to arise from difference in pressure or an actual "squeeze" of bone marrow tissue resulting from compression of bubbles which is so rapid that body fluids cannot immediately replace the suddenly diminished gas volume within the bone cortex Recent reports of characteristic lesions in bone [1] appearing in caisson workers support the view that the symptoms giving rise to bends originate, in part at least, from ischemic changes in bone Kahlstrom Burton and Phemister, Coley and Moore [3] and Rendich and Harrington [4] describe lesions in diaphyses and epiphyses of long bones complicated by joint involvement and attributed to aseptic necrosis of bone or interference with nutrition occurring secondary to the interruption of blood supply by liberated nitrogen gas

However, the etiological relationship between the presence of these lesions and embolic injury must be corroborated by additional findings and animal experiments before final conclusions can be drawn

Macro- and Micro-scopic Observations—In dogs rapidly decompressed from high atmospheric pressure (60 pounds gage) small bubbles can be observed first circulating rapidly through cutaneous arteries and veins and later bubbles of gradually increasing size are found to slow down and eventually stop circulation

In monkeys fitted with leucite calvaria according to the method of Pudenz and Sheldon [6] the formation and movement of bubbles in the cerebral blood vessels can be observed following rapid decompression

Wagner [7] observed through a Forbes window the movement of gas bubbles in the pial blood vessels of cats The bubbles always appeared first in the arteries and later as the blood flow decreased in the veins

per cent were delayed beyond one hour Below is shown the time of onset of symptoms in 547 cases

1– hrs — 5 cases	10–11 hrs — 2 cases
–3 hrs — 108 cases	11–1 hrs — cases
3–4 hrs — 69 cases	12–13 hrs 1 case
4–5 hrs — 38 cases	13–14 hrs — 1 case
5–6 hrs — 6 cases	14–15 hrs — cases
6–7 hrs — 16 cases	15–16 hrs — 1 case
7–8 hrs — 13 cases	16–17 hrs — 1 case
8–9 hrs — 4 cases	17–18 hrs — 1 case
9–10 hrs — 6 cases	18–19 hrs — 1 case

Levy[2] has reported similar data In a series of 37 naval dives of less than 55 minutes exposure it is of interest to note that the onset of symptoms was delayed not infrequently beyond one hour and in one case 7 hours despite the short decompresison time of less than three minutes duration

Effect of Exercise and Other Variable Affecting Bubble Formation —The factors responsible for bubble formation after exposure to high pressure or to high altitude fall into two groups In the first are conditions which increase gas content of tissues namely the amount of fat the degree and duration of exposure to pressure the amount of work performed and in rapid ascent to high altitudes, exercise which among other effects serves to introduce more carbon dioxide into the circulation In the second group are variables affecting the circulation of blood and the transport of gas from the tissues Thus age, time of day temperature, fright injury of tissue and the post alcoholic state all affect what may be termed effective blood flow ' through tissue

In the numerous exposures in the low pressure chamber to simulated altitudes above 30 000 feet the circulatory factors have carefully been evaluated That age is a factor in the sense that an individual of 18 years is less susceptible to bends than an individual of 25 years this suggests the importance of adequate circulation and the influence of metabolic rate The findings in rapid decompressions to simulated high altitudes that bends are more apt to occur in the morning than in the afternoon that fright produces peripheral vasoconstriction to interfere with gas transport and that bends frequently occur at the site of old injury these tend to emphasize the importance of the factor of effective peripheral blood flow and serve to explain not only the variation between individuals but in the same individual when he is subjected to the stress

TABLE III

PERCENTAGE INCIDENCE OF SYMPTOMS AND SIGNS OF DECOMPRESSION SICKNESS[532]

	Caisson Workers			Divers
	Heller Mager Von Schrotter	Keays	Levy	U S Navy
Total No of symptoms	245	3692		1,76
Number of patients	198	—	680*	159
Central nervous system				
Brain				
Hemiplegia		0.11		
Asphasia	0.4			1.14
Auditory disturbances				
Menieres symptom complex	5.9			
Deafness	0.8			
Visual disturbances				5.11
Vertigo	16.3	5.33	6.5	7
Unconsciousness		0.46		1.14
Spinal cord				
Sensory disturbances	4.2	1.00	1.6†	
Motor paralyses	11.7	0.90		0.57
Combined		0.26		
Cardio respiratory system				
Chokes	5.6	1.62	0.1	3.98
Substernal distress				
Asphyxia				
Condition of shock prostration		1.6		
Extremities shoulders and hips				
Pain (bends)	69.6	89.00	91.7	16
Numbness				
Weakness				
Skin manifestations				
Rash itching				6.4
Permanent injury (No of men)	6			
Death (No of men)		0		0

* 1 361,461 decompressions † Central nervous system involvement

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brings about rapid recovery even following paraplegia Insufficient recompression may be followed by residual symptoms of many months duration This type of injury is said to be common in the older Greek sponge divers in Florida

There is a remarkable lack of cerebral involvement even under conditions of widespread embolism Vertigo deafness occasional aphasia and transient visual disturbances have been recorded In contrast with spinal cord lesions permanent impairment referable to lesions of the brain is rare

Conditions giving rise to symptoms similar to those associated with involvement of the spinal cord in decompression sickness are tabes dorsalis and arteriosclerosis of the terminal aorta involving the lumbar segmental arteries

Chokes and the Shock Syndrome.—The most interesting manifestation of decompression sickness is a type of asphyxia designated most aptly by the early caisson workers as "chokes" In comparison with bends chokes occur less frequently since apparently they require the accumulation of quantities of gas moving from the arterial circulation and extravascular tissues into the large veins the right side of the heart and pulmonary vessels Thus several hours of complete well being following decompression may elapse before the appearance of symptoms The earliest symptom of chokes namely a sensation of substernal distress felt only during deep inspiration and especially during inhalation of tobacco smoke serve to elicit paroxysmal coughing This sign has proved to be invaluable as an indication that bubbles are present in pulmonary blood vessels The sensation of substernal distress may be only transient, or it may progress to frank asphyxia Normal breathing may become shallow, rapid and then dyspneic the skin cyanotic or ashen gray cold and clammy The pulse beat at first slow and pounding becomes thready Paroxysmal attacks or coughing or true chokes may precede loss of consciousness The picture presented is one of "shock" and represents a transformation from a state of health and vigor within a period usually of several hours to one of incapacitation without any apparent trauma being inflicted upon the individual It is this condition that not only frequently supervenes in divers, when the premonitory symptoms of bends are ignored and treatment delayed but may be responsible also for circulatory collapse and deaths which occasionally occur following too rapid decompression in the low pressure chamber (altitude decompression sickness)

of decompression There are the same difficulties in ascertaining individual susceptibility to decompression sickness in divers as in aviators In caisson work and diving empirical data establish for man the importance of age, degree of obesity, the post-alcoholic state, the effect of temperature and the influence of exercise during the pressure exposure Conclusions can not be drawn regarding other factors Of greatest importance, however, is the question of the effect of exercise during or following the decompression period Physicians[38] with experience in caisson work have in fact, pointed out the value of exercise following decompression, and divers routinely have taken some exercise on the "stage" during decompression Recent tests by Van Der Aue and his co-workers[39] indicate that exercise following exposure in high pressure atmospheres also increase susceptibility to bends

Detailed Symptomatology

Bends—The most common manifestation of compressed air illness is a dull, throbbing type of pain gradual in onset, progressive and shifting in character and frequently felt in the joints or deeply in muscles and bones Pains of this nature are referred to as "bends", a term established by usage to denote a well recognized clinical entity Prior to the onset of pain there may be, particularly in the joints, paresthesia frequently described as numbness or merely an awareness that "something is not right" Skin temperature may fall as the part involved becomes blanched in appearance In association with bends and chokes fatigue may take the form of an exhausting malaise combined with chills fever and sweating Minor symptoms such as skin rash and pruritus occur frequently, if the skin is chilled during decompression

Paralysis—The most serious complication of decompression sickness is paralysis Dogs rapidly decompressed from high pressures and then only partially recompressed (to a degree that prevents death from asphyxia) usually develop paralysis of the hind legs foot drop a spastic type of gait and paralysis of the bladder musculature[40]

In men a similar spastic paraplegia or monoplegia involving the lower extremities may be preceded or associated with knife-like pains around the chest and pain in the abdomen and lumbar areas radiating toward the lower extremities These sensory disturbances may be so severe as to cause sudden collapse Immediate and prolonged recompression usually

Empirical Diving Data With Reference to Decompression Time

Graphical Presentation of Data in Diving Tables—It is observed that an exposure of 30 minutes at a depth of 40 feet requires minimal decompression (Fig 1)[41] If longer exposures are carried out at the same depth the decompression time required increases linearly with exposure time This graphic method used by Van Der Aue may prove to be the key for the ultimate formulation of correct decompression tables It is observed that as depth increases the slopes of the lines decrease and the rate of decrease eventually may prove to be constant

TABLE IV

Exposure Times in Minutes at Various Depths for Work Dives Followed by Continuous Ascent at Rate of 5 Feet per Minute (Minimal Decompression)

Depth (ft)	Exposure Time in Minutes: U S Navy Tables Diving Manual 19 3	Exposure Time in Minutes: Experimental Diving Unit Tests†
38	—	* 0 to 1440
40	[illegible]	05
50	8	10
60	55	[illegible]
70	43	
85	35	40
90	30	3
100	5	[illegible]
110	20	
120	18	18
130	15	15
140		13
150		11
160	—	9
170		7
180	—	5
190	—	—
200	—	—

* Applies to routine naval diving operations

† Tests made in a wet pressurized tank. Work consisted of weight lifting 2500 ft lb/min for exposures of one hour duration or less and 1250 ft lb/min for exposures of more than one hour[48]

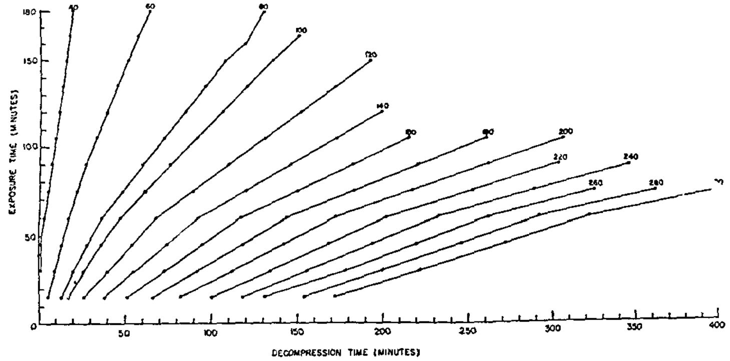


Fig 1 The time required for decompression in relation to the diving exposure time is plotted for various depths ranging from 40 to 300 ft At a depth of 300 ft for example approximately 400 minutes decompression are required for a dive of approximately 50 minutes duration (Plotted by Van Der Aue Experimental Diving Unit Naval Gun Factory Washington D C)

ing Manual tables[42] This is in striking contrast with figure 1 representative of air decompression data

Surface Decompression —Surface decompression is the procedure of bringing a diver from the sea bottom to the surface with decompression limited to the first stop in the water followed immediately by recompression in a chamber and subsequent decompression according to the diving tables beginning with and repeating the first stop[43 44]

This procedure was employed first by Saunders in the salvage of the submarine S 51 in 19 5 because cold water and tides rendered decompression in the open sea impractical In 1939 it was employed extensively in the salvage operations required to raise the U S S Squalus[4] Surface decompression permits the elimination of excess gas from the body tissues under ideal conditions that is with the diver warm at rest and under observation The danger of surface decompression lies in the formation of extensive gas embolism during the interval between the removal of the diver from the water and his subsequent recompression on the surface The U S Navy Diving Manual (1943) gives the following limits of depths and exposure for surface decompression

Feet	Minutes
100	85
110	75
120	60
130	55
140	45
150	40
170	30

Treatment of Decompression Sickness and Air Embolism

Basic Principles —The prime objective in treatment of decompression sickness is the rapid restoration of normal blood supply by immediate recompression which serves to reduce the size of the gas emboli in proportion to the amount of pressure applied Perhaps there is no therapeutic procedure more effective than recompression as applied to the asphyxiated pulseless, cyanotic patient whose blood stream is filled with multiple gas emboli Even patients presenting incipient lesions of the spinal cord have made complete recovery following immediate and prolonged recompression

Long periods of time however are required for the absorption and

For any given depth decompression sickness may occur, if decompression time lies to the left of a given depth line In the Haldane tables however there is a large safety factor as indicated by more recent data obtained in U S Navy tests (Table IV) Possible discrepancies in air diving decompression tables are reflected in irregularities in the linear

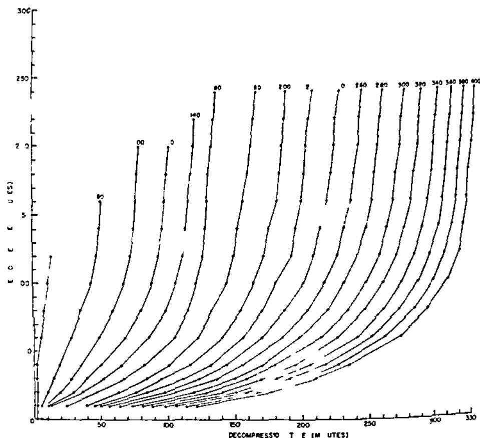


Fig 2 The helium oxygen decompression tables are plotted in the manner indicated in Figure 1

delineation Further, as exposure time increases a uniform safety factor can be applied by decreasing the slope of the lines

Graphic Representation of Decompression Tables when Helium Oxygen Mixtures Are Used —The fact that very little additional decompression time is required for helium-oxygen dives after an exposure of about 100 minutes is emphasized by the curves in Fig 2 based on Di

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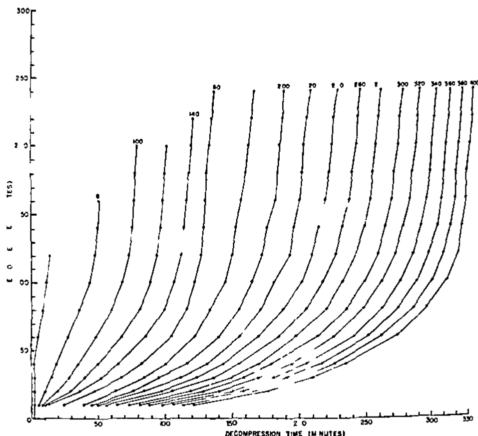


Fig   The helium-oxygen decompression tables are plotted in the manner indicated in Figure 1

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TABLE V

Treatment of Caisson Disease and Air Embolism

	BENDS —PAIN ONLY		SERIOUS SYMPTOMS	
DESCEND 25 ft/min ASCEND 1 min between stops	Pain relieved at depth LESS THAN 66 ft Use table 1A if O_2 is not available	Pain relieved at depths GREATER THAN 66 ft Use table 2A if O_2 is not available If pain does not improve within 30 min at 165 ft the case is probably not bends Decompress on Table 2 or 2A	Serious symptoms include any one of the following 1 Unconsciousness 2 Convulsions 3 Weakness or inability to use arms and legs 4 Any visual disturbances 5 Dizziness 6 Loss of speech or hearing 7 Severe shortness of breath or chokes	
			Symptoms RELIEVED within 30 min at 165 ft Use table 3	Symptoms NOT RELIEVED within 30 min at 165 ft Use table 4

STOPS		TIME IN MINUTES UNLESS OTHERWISE INDICATED					
Lbs	Ft	Table 1	Table 1A	Table 2	Table 2A	Table 3	Table 4
73.4	165			30 (Air)	30 (Air)	30 (Air)	30 to 120 (Air)
62.3	140			12 (Air)	12 (Air)	12 (Air)	30 (Air)
53.4	120			12 (Air)	12 (Air)	12 (Air)	30 (Air)
44.5	100	30 (Air)	30 (Air)	12 (Air)	12 (Air)	12 (Air)	30 (Air)
35.6	80	12 (Air)	12 (Air)	12 (Air)	12 (Air)	12 (Air)	30 (Air)
26.7	60	30 (O_2)	30 (Air)	30 (O_2)	30 (Air)	30 O_2 or Air	6 hrs (Air)
22.3	50	30 (O_2)	30 (Air)	30 (O_2)	30 (Air)	30 O_2 or Air	6 hrs (Air)
17.8	40	30 (O_2)	30 (Air)	30 (O_2)	30 (Air)	30 (O_2 or Air)	6 hrs (Air)
13.4	30	↑	60 (Air)	60 (O_2)	2 hrs (Air)	2 hrs (Air)	First 11 hrs AIR Then 1 hr O_2 or AIR
8.9	20	5 (O_2)	60 (Air)	↑	2 hrs (Air)	2 hrs (Air)	First 1 hr AIR Then 1 hr O_2 or AIR
4.5	10		2 hrs (Air)	5 (O_2)	4 hrs (Air)	2 hrs (Air)	First 1 hr AIR Then 1 hr O_2 or AIR
SURFACE		↓	1 min (Air)	↓	1 min (Air)	1 min (Air)	1 min (O_2)

If symptoms recur DURING treatment, recompress to depth of relief but never less than a depth of 30 ft and complete decompression from this depth according to table 4.

If dizziness, nausea, muscular twitching or blurring of vision occurs while breathing oxygen remove mask and proceed as follows (a) if using table 1 complete remaining stops of table 1A (b) if using table 2 complete remaining stops of 2A (c) if using table 3 complete remaining stops of table 3 breathing air. At the discretion of the physician oxygen breathing may be resumed at the 40 and 30 foot stops for a total of 90 minutes if using table 1 or 3 and 150 minutes if using table 2.

elimination of gas bubbles The absence of symptoms in a patient under recompression treatment does not signify freedom from "silent gas bubbles The appreciation for the need of prolonged recompression underlies any regimen for successful therapy

The tabular outline (Table V)[11] serves as a guide for recompression treatment and incorporates the following features developed from principles formulated by Behnke and Shaw[10] and Yarbrough and Behnke[1], (1) a 30 minute period at maximal depth (b) the use of oxygen when available (c) prolonged recompression for 24 or more hours in serious cases It is emphasized that the condition of the patient governs therapy rather than rigid adherence to a tabular outline The tables however, represent the best practice at the present time on the basis of extensive experience gained at the Experimental Diving Unit, Navy Yard, Washington D C

Specific Treatment Procedures as They Apply to the Manifestations of Decompression Sickness —Bends —In the mild cases of decompression sickness characterized by "bends" and comprising the majority of cases the minimal pressure applied is 44 5 psi (gage) equivalent to a diving depth of 100 feet (treatment tables 1, 1A in Table V) Relief of symptoms may occur at a lower pressure, but the additional compression reduces the size of bubbles to one-fourth of their surface volume and facilitates their absorption

Occasionally, if recompression is delayed, or if excessive bubble formation is present pressure in excess of 44 5 psi may be required for relief of pain (treatment table 2 A in Table V) The persistence of pain at a pressure depth of 165 feet is indicative that some condition other than "bends" exists unless residual tissue injury is present Some relief from "bends" pain as the pressure is applied is the almost invariable response The one exception is the occasional condition characterized by an increase in severity of symptoms as the pressure is applied The basis for this aggravation of pain appears to be the too rapid application of pressure resulting in the tendency of the bubbles in the bone marrow to be reduced faster than those in the blood, and tissue fluids are replenished with the consequent squeezing of the bone tissue The aggravation of pain can be prevented by slow application of pressure

Asphyxia, Circulatory Collapse, Paralysis —For the serious cases of decompression sickness recompression is limited to a pressure of 73 4 psi (gage) equivalent to a depth of 165 feet At this pressure the bubble has been reduced to 17 per cent of its surface volume Higher pres

TABLE V

Treatment of Caisson Disease and Air Embolism

	BENDS—PAIN ONLY		SERIOUS SYMPTOMS	
DESCEND 25 ft/min ASCEND 1 min between stops	Pain relieved at depths LESS THAN 66 ft Use table 1A if O_2 is not available	Pain relieved at depth GREATER THAN 66 ft Use table 2A if O_2 is not available If pain does not improve within 30 min at 165 ft the case is probably not bends Decompress on Table 2 or 2A	Serious symptoms include any one of the following 1 Unconsciousness 2 Convulsions 3 Weakness or inability to use arms and legs 4 Any visual disturbances 5 Dizziness 6 Loss of speech or hearing 7 Severe shortness of breath or chokes	
			Symptoms RELIEVED within 30 min at 165 ft Use table 3	Symptoms NOT RELIEVED within 30 min at 165 ft Use table 4

STOPS		TIME IN MINUTES UNLESS OTHERWISE INDICATED					
Lbs	Ft	Table 1	Table 1A	Table 2	Table 2A	Table 3	Table 4
73.4	165			30 (Air)	30 (Air)	30 (Air)	30 to 120 (Air)
62.3	140			12 (Air)	12 (Air)	12 (Air)	30 (Air)
53.4	120			12 (Air)	12 (Air)	12 (Air)	30 (Air)
44.5	100	30 (Air)	30 (Air)	12 (Air)	12 (Air)	12 (Air)	30 (Air)
35.6	80	12 (Air)	12 (Air)	12 (Air)	12 (Air)	12 (Air)	30 (Air)
16.7	60	30 (O_2)	30 (Air)	30 (O_2)	30 (Air)	30 (O_2 or Air)	6 hrs (Air)
22.3	50	3 (O_2)	30 (Air)	30 (O_2)	30 (Air)	30 (O_2 or Air)	6 hrs (Air)
17.8	40	30 (O_2)	30 (Air)	30 (O_2)	30 (Air)	30 (O_2 or Air)	6 hrs (Air)
13.4	30	↑	60 (Air)	60 (O_2)	2 hrs (Air)	12 hrs (Air)	First 11 hrs AIR Then 1 hr O_2 or AIR
8.9		5 (O_2)	60 (Air)	↑	2 hrs (Air)	2 hrs (Air)	First 1 hr AIR Then 1 hr O_2 or AIR
4.5	1		2 hrs (Air)	5 (O_2)	4 hrs (Air)	[illegible] hrs (Air)	First 1 hr AIR Then 1 hr O_2 or AIR
SURFACE		↓	[illegible] min (Air)	↓	1 min (Air)	[illegible] min (Air)	[illegible] min (O_2)

If symptoms return DURING the time, recompress to depth of relief but never less than a depth of 30 ft and complete decompression from that depth according to table 4.

If during [illegible] itching or blurring of vision occur while breathing oxygen remove mask and proceed as follows (a) if using table 1 complete remaining stops of table 1A (b) if using table 2 complete remaining stops of 2A (c) if using table 3 complete remaining stops of table 3 breathing air. At the discretion of the physician oxygen breathing may be resumed at the 40 and 30 foot stops for total of 90 minutes if using table [illegible] or 3 and 150 minutes if using table 2.

sures, as they affect bubble size, improve circulation, and they prolong decompression at level where oxygen cannot be breathed safely

The practice of prolonged immersion in compressed air, colloquially termed "the overnight soak", has proved to be the conclusive method of terminating treatment The patient is permitted to sleep, and the bubbles have adequate time for absorption Should there by any question of involvement of the central nervous system, the prolonged compression treatment is routinely put into effect

For the moribund patient the pressure level following the 2-hour treatment at a depth equivalent to 165 feet is decreased in 30 minute stages to 60 feet (treatment table 4 in Table V) There should be no hesitancy in continuing treatment at the 60-foot level for a period of days if signs of severe circulatory impairment or paralysis persist It is unlikely, however, that the time periods given in treatment table 4 in Table V will be exceeded

Air Embolism—This accident (in submarine escape) always must be regarded as serious The symptoms are referable to the central nervous system and the circulation, and therefore, treatment tables 3 and 4 in Table V are applicable Symptoms have recurred when inadequate recompression has been given and individuals believed to be "cured" by the initial treatment have been rushed to the recompression chamber in a state of collapse

Prior to ascending from any level the patient's ability to stand and walk the length of the chamber should be tested This test should be made routinely before leaving the maximal depth, at the completion of the 60- and 30-foot stops and at the end of the recompression treatment

Complications Arising During the Course of Treatment—*Oxygen Toxicity*—In the resting individual severe symptoms of oxygen poisoning rarely occur during the first two to three hours at depth of 60 feet If, however during the course of oxygen inhalation, dizziness nausea muscular twitching, blurring of vision, tremor, extreme irritability or apprehension occur, oxygen should be discontinued and the following procedure should be put into effect (a) if using treatment table 1 in Table V complete remaining stops of treatment table 1A, (b) if using treatment table 2, complete remaining stops of treatment table 2A, (c) if using treatment table 3, complete remaining stops of treatment table 3 breathing air At the discretion of the physician oxygen breathing may be resumed at the 40 and 30 foot stops for a total of 90 minutes, if using treatment tables 1 or 3, and for 150 minutes if using table 2

Spontaneous pneumothorax—The sudden onset of thoracic pain

accompanied by respiratory embarrassment as the chamber pressure is reduced suggests the complication of pneumothorax Thoracocentesis in the pressure chamber may be required in order to permit the completion of treatment It is emphasized that vigorous employment of the Valsalva and other procedures in order to equalize pressure within the middle ear spaces should be interdicted

Recurrence of Symptoms—Should symptoms recur following the use of treatment tables 1, 1A, 2 or 2A, recompress the patient to a depth giving relief If relief occurs at depths less than 30 feet, take the patient to 30 feet and then decompress from the 30 foot stop to surface according to treatment table 3 If relief occurs deeper than 30 feet remain at the depth of relief for thirty minutes and then complete the remaining stops using treatment table 3 and air throughout If symptoms recur after following treatment table 3 take the patient to the depth necessary to relieve symptoms If this depth is greater than 30 feet keep the patient at this depth for thirty minutes and complete treatment as outlined by table 4 If the depth of relief is less than 30 feet take the patient to 30 feet and complete treatment as outlined by table 4

Adjuncts to Treatment—Judicious injection of glucose saline and plasma may be required for severely injured patients in order to counteract the effect of hemoconcentration

The presence of appreciable quantities of gas in the blood stream places a severe load on the right ventricle and leads to dilatation Following signs of circulatory embarrassment or collapse it is probable that the right ventricle is injured and all therapy must be directed toward the conservation of the right ventricular musculature

Large accumulations of gas in pulmonary vessels may lead to some degree of pulmonary edema The probability of pneumonitis following severe decompression sickness and the presence of lung injury following accidents with the submarine escape appliance may be followed by pneumonia

Frequent Errors in Diagnosis and Treatment—Diving history is replete with examples of obvious errors in diagnosis and treatment The fact that bends may occur only once in a series of 100 similar dives is not generally appreciated Most of the errors can be attributed to

(a) Failure to apply the pressure test in doubtful cases Although muscular and ligament injury unrelated to bends tenosynovitis fractures, and appendicitis have occurred during and immediately following recompression, it is safe practice to apply a pressure test of at

least a few pounds per square inch in all doubtful cases to eliminate the possibility of "bends"

(b) Delayed recompression This mistake usually is due either to negligence on the part of the patient in reporting early symptoms or to failure of the diving supervisor or attending physician to keep divers in the vicinity of the pressure chamber Apart from "bends" pain substernal distress upon deep inspiration and irritation caused by tobacco smoke are to be looked for as early signs of "chokes"

(c) Failure to treat adequately the serious cases according to treatment tables 3 or 4 in Table V gives rise to recurrence of symptoms and necessitates repeated recompressions The apparently complete recovery of patients during the early stages of recompression may lead to the belief that the gas bubbles have been eliminated before this actually has been accomplished Experience has emphasized that long periods of compression are required for gas elimination once bubbles have formed The "overnight soak" at pressures equivalent to depths of 30 to 60 feet has proved to be most effective

(d) Failure to keep the 'treated' patient near the chamber for a 24-hour period This error has been responsible for the occasional collapse or death of divers who were considered to have had adequate treatment

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CHAPTLR XIX–D

MOTION SICKNESS

By R S SCHWAB

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INTRODUCTION

Seasickness is a problem with which the general practitioner is little concerned but on shipboard the doctor finds it the chief complaint Air sickness is a problem for the commercial air line passengers and hostesses but is of little concern to others Both these illnesses or *complaints are essentially the same thing and along with car train and* swing sickness are now known by the general term of Motion Sickness

With the inevitable increase in commercial air and sea travel since the last war more and more persons will become aware of motion sickness as a personal medical problem Therefore in general practice there *will be an increasing number of requests from the susceptible for advice* and medicine to prevent discomfort and illness on undertaking such trips

RECENT STUDIES

By the beginning of World War II there were a large number of clinical papers on this subject covered in a review by this author in 194 [1] Since that time and up to the present an extraordinary amount *of expert investigation has been done by* the clinical and physiological teams of the Armed Forces of the Allies and this material is now available and appearing here and there in excellent published sum

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INTRODUCTION

Seasickness is a problem with which the general practitioner is little concerned but on shipboard the doctor finds it the chief complaint. Air sickness is a problem for the commercial air line passengers and hostesses but is of little concern to others. Both these illnesses or complaints are essentially the same thing and, along with car, train and swing sickness, are now known by the general term of Motion Sickness.

With the inevitable increase in commercial air and sea travel since the last war, more and more persons will become aware of motion sickness as a personal medical problem. Therefore in general practice there will be an increasing number of requests from the susceptible for advice and medicine to prevent discomfort and illness on undertaking such trips.

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maries[3,4,5] The military aspects of this problem are outside the scope of this paper but were a vital part of the protection of soldiers in small vessels or aircraft landing on hostile shores In addition the prevention and treatment of seasickness in naval personnel, especially in key men such as radar operators on small ships in rough weather, was an important task An issue in the selection of aircraft personnel or the crews of fast small craft such as motor torpedo boats (P T) was the weeding out of susceptible men who by motion sickness would impair not only their efficiency but also the safety of the craft and the crew It was along these lines that most of the elaborate and careful investigation was carried out[6]

Motion sickness produces its effects through a subtle combination of disturbances of vestibular visual and olfactory perceptions plus psychogenic factors involving all sorts of conditioning experiences in the past It is because of this complication of etiological backgrounds that in spite of the tremendous amount of work done in the war years the problem still is unsolved

It is generally agreed that the motion of a ship plane or other craft reaches the brain through the vestibular apparatus in the internal ear Animals deprived of these organs cannot be made ill in swings or other motion devices[7]

There is no good evidence that susceptible persons have abnormal or hypersensitive labyrinths[8] In a group of unselected humans say the first 100 to pass a certain street corner 40 or 50 would be seasick on a ship in rough weather In very rough weather 75 would be affected and in extreme situations nearly all of them If 100 lobster fishermen were placed on a small ship in a rough sea perhaps only 10 would be ill because here a sort of artificial selection is involved This makes many of the war statistics on the incidence of motion sickness in any particular group of personnel such as flyers paratroopers, etc , interesting but not indicative of its incidence in the general population

It is important here to re emphasize a preliminary classification made by this author in his original paper in 1942[1] There are essentially two types of persons that suffer from seasickness (1) The proverbial *land lubber* who is made ill by the usual motion of cars trains swings small boats large ships and planes is prostrated by this illness and remains acutely ill until motion subsides He was termed type #1 by this author and is a person with an inexplicable predisposition to all forms of motion sickness In such individuals there is also a high incidence of mild symptoms of psychoneurosis (78 per cent in a series of 1 5)

(2) The ordinary person without the constitutional susceptibility who gets seasick when the weather is rough and who usually gets over it with the help of medication or develops through habituation a tolerance to this motion In this group which is called type # there is a low incidence of psychoneurotic traits (2 per cent in a series of 150)

In any attempt to prevent the onset of motion seasickness it is obvious that the type #1 individuals are going to be the more difficult to help These type #1 patients were most often ill in spite of preventive drugs and they responded less satisfactorily to medication after they became ill In many cases during war conditions it was necessary to remove them from their ships and place them on shore in order that they might function efficiently Therefore a physician who is prescribing preventive treatment for a potential traveler should take a careful history of his susceptibility to any and all forms of motion sickness As stated before this group had a rather high incidence in neurotic traits and it would be expected that reassurance and suggestion would be more efficient in these patients than in others In the type # individuals the problem is much simpler and the effect of reassurance and suggestion less striking

During the war a great deal of effort was made to devise machines to simulate the motion of ships and aircraft and thereby provide test situations to eliminate susceptible individuals and to study the physiology of motion sickness[9] Swings usually 18 feet high with 60 arcs were the simplest Complicated rockers bringing in roll pitch and vertical motion in any degree desired were the more elaborate None of these machines gives the same general atmosphere as a stuffy cabin on a crowded vibrating ship in a rolling sea In spite of their obvious limitations it was shown that histories of sea and air sickness correlated in a general way with sickness on these testing machines[10] and their use in assessing the effectiveness of antiseasick remedies and in eliminating susceptible personnel was proven Most men able to survive for 30 minutes on such a swing did not get ill on a destroyer but not all and conversely some swing sick men made good sailors[5] The reader is referred to the excellent summary by the Montreal group[3] for details of some of this important work

SYMPTOMS

The earliest symptom associated with motion sickness is a lack of interest in what the subject is doing This is often associated with a loss of inclination for tobacco and a distaste for food About the same

they need not be used Smoking usually accentuates sea or air sickness and is best avoided In fact, the earliest sign of motion sickness may be lack of the usual desire for tobacco and may indicate when to begin preventive measures

If preventive capsules are used, they should be taken early and regularly every 4 or 5 hours for 2 to 3 days, gradually reducing the number

In preventing or in treating motion sickness, the drugs used should (1) reduce vestibular sensitivity and sensory stimuli, in general, barbiturates are excellent, bromides less specific, (2) relax the pylorus and reduce both gastric and salivary secretion Antispasmodic drugs such as atropine, hyoscine, hyoscyamus, syntropan, benzedrine and others do this The mixture of the two barbiturates and atropine drugs, therefore, is both rational and effective In war the problem of maintaining full coordination, awareness, vision and strength as well as allowing the maximum effect of both atropine and sedation, made this exceedingly complicated It was naturally inefficient and even dangerous to have troops landing on a beach with impaired vision or suffering from the sedative effects of various drugs so that they would be sleepy or ataxic On the other hand, in peace time fortunately there is little harm in being drowsy, relaxed and even having a temporary impairment of vision, if the symptoms of motion sickness are prevented This, of course applies only to passengers of aircraft or ships It is, therefore, possible to take larger amounts of the sedative drugs in the preventive tablets and even spend a greater part of the first day or two of a voyage in a somnolent state A mild safe preventive tablet containing 0 3 mgm (gr 1/200) of hyoscine and 15 mgm (gr ¼) of phenobarbital may be given safely every 4 to 6 hours for 1 to 2 days It is usually considered best to get an initial effect and then reduce the dose To do this the initial dose would be two of the above tablets or capsules (formula A)

A mixture of hyoscyamine hydrobromide 0 8 mgm (gr 1/75) and 0 3 mgm hyoscine (gr 1/200) is as efficient as more hyoscine alone and less unpleasant as to dryness of mouth blurred vision and light-headedness This mixture also contains more phenobarbital It should not be taken more than 4 to 5 times a day and for no more than 2 to 3 days (formula B)

Much evidence in the war showed that various combinatians depended on the hyoscine and some advocate its use alone (formula C)

The United States Army used a formula called MSP (motion sickness preventive) containing as shown in the table (formula D) both hyoscine mgm 0 4, atropine mgm 0 3 and amytal mgm 130 Benze

drine could be added (mgm 5) If large numbers are taken over dosage from amytal is possible

Formulae E and F are mixtures used by this author with considerable success in spite of the specific data that hyoscine is a better preventative than atropine

Formula G is one published by Noble[1] and recommended by the National Research Council of Canada Its main ingredient is an acid of a new barbiturate (V 1) put out by Abbott Drug Company Noble feels that it is at least as good as any and has a more prolonged effect than the alkaloids above He advises 2 tablets at the start of the trip and 1 every 8 hours thereafter for no more than 4 to 5 days

In summary the use of preventive tablets is effective in two-thirds of the cases when used early and regularly but it must not be forgotten that one fourth to one third of moderately susceptible people are suggestable enough to be protected by placebos[5]

The following formulae are suggested in order of strength

A	Hyoscine hydrobromide	mgm	0.3	(gr 1/200)
	Phenobarbital	mgm	15.0	(gr ¼)
B	Hyoscyamine hydrobromide	mgm	0.8	(gr 1/75)
	Hyoscine hydrobromide	mgm	0.3	(gr 1/200)
	Phenobarbital	mgm	30.0	(gr [illegible])
C	Hyoscine hydrobromide	mgm	0.6	(gr 1/100)
D	Hyoscine hydrobromide			
	Amytal	mgm	130.0	(gr)
	Atropine sulfate	mgm	0.3	(gr 1/ 00)
E	Atropine sulfate	mgm	0.6	(gr 1/100)
	Phenobarbital	mgm	30.0	(gr [illegible])
	Benzedrine sulfate	mgm	5.0	(gr 1/1)
F	Atropine sulfate	mgm	0.6	(gr 1/100)
	Pentobarbital	mgm	100.0	(gr 1[illegible])
G	Hyoscine hydrobromide	mgm	0.1	(gr 1/600)
	Hyoscyamine hydrobromide	mgm	0.3	(gr 1/200)
	Ethyl b methyl allyl theobarbituric acid	mgm	130.0	(gr)

Treatment

It is obvious that, since the preliminary symptoms of nausea and vomiting are accompanied by gastric hypersecretion, salivation and spasm of the pylorus, the ingestion of pills or capsules by mouth to eliminate the symptoms would be futile Substances taken in this way whether they be solid or liquid, simply add to the mass of rapidly accumulating fluid in the stomach whose outlet is closed by the spasm of the pylorus Absorption of these drugs will not occur in the stomach and they will be lost with the ensuing vomiting In other words after the symptoms of motion sickness have been firmly established, the ingestion of oral medication usually is a waste of time The only treatment once vomiting starts is subcutaneous or intravenous injection of the proper drugs The use of preventive drugs taken by mouth is practical and efficient only when the pylorus is open and the direction of peristalsis is normal

If motion sickness comes on the following is the best procedure

1. Lie down preferably in a well ventilated place, and keep warm
2. Keep up a moderate intake of fluids (cold water) and crackers in small amounts
3. Take a sedative or motion sickness remedy parenterally if possible
4. Avoid reading and smoking
5. Keep the eyes closed
6. Avoid conversation about seasickness
7. Try to accept the onset of the illness as of no consequence in that concern or worry over it only aggravates the difficulty
8. Try in a few hours' time to re establish some sort of habituation to motion
9. If nausea and vomiting ensue let them happen without resistance as often when the stomach is empty the nausea will subside
10. Keep trying to get down fluids and crackers as more often than not encouragement to eat will re-establish normal peristalsis in the right direction
11. Avoid fatty greasy foods

If the above fail as is not uncommon the best drug to use is intramuscular atropine (0 6 mgm gr 1/100) or hyoscine, 0 6 mgm gr 1/100) repeating the initial dose in 4 to 6 hours and thereafter one half of this dose (0 3 mgm gr 1/200) every 6 to eight hours as needed Mor

phine which often causes nausea interferes with normal direction of peristalsis depresses the cough and respiration and usually is contra indicated Sedation in addition may be given such as sodium luminal 120 mgm (gr) subcutaneously If much vomiting occurs with dehydration and acidosis it may be wise to give saline by vein or subcutaneously

It is important to keep encouraging the subject to eat and drink fluids move about sit up get up and out of his bed as soon as he can Often appetite peculiarities appear in a moderately seasick patient and these should be lavishly indulged if possible For example, if it is iced champagne or white turkey meat or ripe olives it is often wise to try to get them and thus start the patient off on some sort of caloric intake by mouth

The following account would be a typical example of a severely susceptible person efficiently controlled along the lines suggested

A 27 year old single female has a seven day mid winter Atlantic crossing to make Her past history shows susceptibility to sickness in swings roller coasters trains cars and elevators On three previous sea trips she was prostrated by illness She avoided air travel after a two hour bout of air sickness between two cities Her apprehension caused her to consult the ship surgeon while the ship was at the pier He had a talk with her reassured her that he would take care of the problem gave her a capsule containing 0 3 mgm (gr 1/200) of hyoscine and 30 mgm (gr 1/) of phenobarbital and instructed her to keep on her feet, walking briskly back and forth on deck as the ship left the harbor (one half hour trip) After passing the last channel buoy a gentle swell brought on the familiar pitch of the ship Soon she lay down on a deck chair Rapid onset of nausea ensued and her companion called the ship s surgeon He assisted her to her cabin which was hot and stuffy where she vomited He gave her a subcutaneous injection of 0 6 mgm (gr 1/100) of hyoscine and saw to it that her cabin was cleaned up and the port hole opened She slept for two hours and awake nauseated and vomited six or seven times A second injection of 0 3 mgm (gr 1/ 00) of hyoscine was given and a plate of cracked ice left by her bedside She slept four hours and awoke feeling better with a dry mouth and thirsty She drank some tomato juice and promptly vomited She was given no further medication until a third episode of vomiting when it was obvious that she was somewhat dehydrated A 1 000 c c normal saline injection was given slowly in the vein and 0 6 mgm (gr 1/100) of hyoscine subcutaneously and crackers and ice were left by her bedside She awoke nibbled crackers drank some ice water which stayed down She now felt better As the day wore on she ate a sandwich and

TREATMENT

It is obvious that, since the preliminary symptoms of nausea and vomiting are accompanied by gastric hypersecretion, salivation and spasm of the pylorus, the ingestion of pills or capsules by mouth to eliminate the symptoms would be futile Substances taken in this way, whether they be solid or liquid, simply add to the mass of rapidly accumulating fluid in the stomach whose outlet is closed by the spasm of the pylorus Absorption of these drugs will not occur in the stomach, and they will be lost with the ensuing vomiting In other words, after the symptoms of motion sickness have been firmly established, the ingestion of oral medication usually is a waste of time The only treatment, once vomiting starts is subcutaneous or intravenous injection of the proper drugs The use of preventive drugs taken by mouth is practical *and efficient only when the pylorus is open and the direction of peri*stalsis is normal

If motion sickness comes on the following is the best procedure

1 Lie down preferably in a well ventilated place and keep warm
2 Keep up a moderate intake of fluids (cold water) and crackers in small amounts
3 Take a sedative or motion sickness remedy parenterally if possible
4 Avoid reading and smoking
5 Keep the eyes closed
6 Avoid conversation about seasickness
7 Try to accept the onset of the illness as of no consequence in that concern or worry over it only aggravates the difficulty
8 Try in a few hours' time to re establish some sort of habituation to motion
9 If nausea and vomiting ensue let them happen without resistance as often when the stomach is empty the nausea will subside
10 Keep *trying to get down fluids and crackers* as more often than not encouragement to eat will re-establish normal peristalsis in the right direction
11 Avoid fatty greasy foods

If the above fail as is not uncommon the best drug to use is intramuscular atropine (0 6 mgm gr 1/100) or hyoscine, 0 6 mgm gr 1/100) repeating the initial dose in 4 to 6 hours and thereafter one half of this dose (0 3 mgm gr 1/200) every 6 to eight hours as needed Mor

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some soup which she retained The next day she was able to dress and go on deck and subsequently developed enough habituation to keep down a light lunch when served on deck She lost six pounds in seven days and was able to eat her last meal aboard in the dining salon

Now this case is fairly typical It shows that seasickness requires a lot of attention and is only partially amenable to therapy It illustrates the need of early medication, fluid requirements and the necessity of compromise with food and rest, but it does represent how trying the problem may be for both passenger and surgeon

SUMMARY

In summary the best way to prevent the disease, of course, is to avoid situations, where a sudden and violent motion is likely, and try to take trips where gradual habituation to the motion can be encountered The general measures mentioned in the text are valuable, and specific drugs are to be prescribed from the formulae included All patients taking medication of this sort should be warned about over-dosage such as excessive dryness of the mouth, extreme somnolence and intolerable blurring of vision With care and the proper instruction in medication some of the prescriptions mentioned are very effective in preventing seasickness in some persons and if it does develop, usually it is of a milder form The physician prescribing preventive tablets must be prepared for a certain number of complete and hopeless failures particularly when he is dealing with the type #1 persons who so often fail to benefit by any treatment whatsoever

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CHAPTER XIX-E

CHRONIC BROMIDE INTOXICATION

By FREDERIC M. HANES

TABLE OF CONTENTS

Synonyms — Bromide poisoning bromidism bromism

Definition — A condition produced by the continuous ingestion of bromides in the presence of either an absolutely or relatively low intake of sodium chloride

INTRODUCTION

Normally the blood contains only a trace of bromide (0 2 to 0 4 mgm per cent) but when bromides are taken repeatedly the bromide ion tend to accumulate in the blood leading under certain conditions to more or less severe intoxication Bromides are among the most frequently prescribed of all drugs but it is unfortunately true that many physicians do not appreciate the danger of bromide poisoning This probably is due to the fact that medical text books have failed in the past to emphasize the condition relegating bromidism to dermatological and psychiatric treatises Less than a fourth of the patients with severe bromide poisoning show a skin rash usually non characteristic and only the severest mental manifestations are referred to the psychiatrist It is the internist and general practitioner who have the opportunity of observing the early evidences of bromide poisoning but all too often this is not considered in their differential diagnosis as a result many puzzling neuropsychiatric

patients (69 2 per cent) had a blood bromide content of 50 to 150 mgm per cent and that 223 (30 8 per cent) showed amounts of blood bromide varying from 150 to 428 mgm per cent

To obtain an approximate estimation of the excessive use of bromides in general medical patients bromide determinations were done on 500 consecutive medical dispensary patients at Duke Hospital Of these 500 64 (13 per cent) had positive blood bromides and 29 (5 8 per cent) had 50 mgm per cent or more 12 (2 4 per cent) had more than 100 mgm per cent 5 (1 per cent) had a blood bromide content of more than 150 mgm per cent The figures quoted in this paper indicate a startlingly high incidence of bromidism both in general medical and institutional patients

Etiology

The patient to whom bromides are given or who takes one of the innumerable patent medicines containing bromides often suffers from some more or less severe underlying condition which manifests itself through the central nervous system The bromide ion when absorbed into the cells of the nervous system depresses their excitability leading to a slowing of all the physical processes Lethargy and drowsiness result and due to a lessened movement heat production and respiration are decreased Bromides exert a depressing effect on the spinal cord inhibiting spinal reflexes and large doses depress the heart and vasomotor centers sometimes lessening arterial tension Both libido and potentia are decreased or abolished The higher cortical centers are affected especially cerebration is retarded speech is slowed articulation is impaired and the threshold for motor cortical responses is depressed The bromides then are efficient sedatives and when used with a full knowledge of their inherent danger among the most useful of drugs

Bromides are absorbed rapidly and can be detected in the urine within a few minutes after they are ingested They like the chlorides are found in largest amount in the blood plasma and to a much less extent in the organs They appear in all the secretions of the body such as saliva tears sweat milk cerebrospinal fluid and as hydrobromic acid in the gastric juice In bromide poisoning the cerebrospinal fluid contains only a little less bromide than does the whole blood After a single dose of 2 grams of bromide about 10 per cent is excreted in the first 24 hours and the remainder over a period of as much as two months This slowness of excretion may result in accumulation to the point of intoxication when bromides are taken continuously with an inadequate sodium chloride

conditions are incorrectly diagnosed and *not a few are committed wrong fully to psychiatric hospitals*

INCIDENCE

Bromide intoxication is a widespread and common condition In the Duke Hospital Clinic many of the severest instances of bromidism have been observed in the families of physicians themselves Our memories are all too poignant of physicians bringing to the clinic a wife or daughter suffering from toxic delirium due to bromide intoxication This is dis tressing enough but it is a real tragedy when such patients are committed, as they often are to a psychiatric institution under the impression that the sufferer has a major psychosis for such a committment still carries with it a stigma in the eyes of the laity It is true that a severe bromide poisoning may conceal an underlying psychosis but in the general practice of medicine this is by no means the rule Many patients with severe bromide intoxication are found to be normal or suffering from a mild neurosis only when bromide has disappeared from the blood In most localities patients are committed to psychiatric hospitals by physicians totally untrained in psychiatric diagnosis It can scarcely be emphasized too strongly that those patients at least who show a toxic confusional psychosis should have a bromide determination done on their urine or blood or both before committment papers are signed The wisdom of this becomes apparent when one examines the experience of psychiatric hospitals

Wagner and Bunbury[1] have reported the results of bromide deter minations upon 1 000 consecutive admissions to the Colorado Psychiatric Hospital Seventy seven (7 7 per cent) patients showed 75 mgm per cent or more of bromide in the blood serum Of these 17 (22 08 per cent) were admitted entirely on account of bromide poisoning and ex hibited no underlying psychotic condition after the elimination of bromide from the blood It is stated by Harding and Harding that from 3 to 5 per cent of admissions to State Hospitals have been found to be due solely to bromide intoxication and that in one private sanatorium 23 4 per cent of the toxic confusional group were admitted solely because of bromide poisoning Reports from many parts of the country [3 4 5] cor roborate the Colorado experience

Hanes and Yates[5] have analyzed a group of 400 patients admitted to Duke Hospital who showed more than 50 mgm per cent of bromide in the blood serum Adopting the arbitrary figure of 150 mgm per cent or more of blood bromide as indicating severe poisoning they found that 177

patients (69 2 per cent) had a blood bromide content of 50 to 150 mgm per cent and that 2.3 (30 8 per cent) showed amounts of blood bromide varying from 150 to 428 mgm per cent

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intake The bromide is not simply added to the normal salt content of the blood but it replaces chloride which is excreted preferentially by the kidneys in a quantity sufficient to maintain the normal salt concentration. It is of practical importance to realize that as bromide accumulates in the blood chloride diminishes the reverse is true also that an excess of chloride reduces the concentration of bromide Hence theoretically the therapeutic exhibition of bromides should be accompanied by a diminished sodium chloride intake but in practice this is accomplished with difficulty On the other hand the continuous ingestion of bromides when the salt intake is low as after operations with liquid or semi solid diets or when the food and salt intake is low from any cause may lead quickly to severe bromide poisoning Under such conditions it is quite possible for a patient to be poisoned in a few weeks by the usual therapeutic dosage of bromides Various conditions such as anemia drug addiction and chronic alcoholism are said to predispose to bromide intoxication

Rylan[6] estimates that in order to maintain the chloride bromide equilibrium in the blood that is that as much bromide should be excreted as ingested the chloride intake should be four times the bromide intake Patients vary greatly in their normal sodium chloride consumption Wuth[7] found that on a uniform hospital diet patients varied in their salt intake from 3 to 15 grams with an average of about 7 grams With the usual dosage of 3 to 4 grams of bromide daily the sodium chloride intake should be 12 to 16 grams in order to maintain a chloride bromide equilibrium

Symptoms

Bromide poisoning may be mild severe and even fatal It is often but by no means always the result of medication to alleviate some underlying mental or physical ailment Bromides are notoriously the resort of the psychoneurotic and it is estimated that more than 200 'patent' medicines containing bromides are on the market They are a frequent ingredient of headache remedies together with acetanilid and caffeine But the widespread occurrence of bromide poisoning can not be blamed entirely upon the vendors of nostrums the medical profession is heavily incriminated Wagner and Bunbury found that 42 per cent of their severely poisoned patients had received the bromide on a physician s prescription The busy doctor who advises the continuance of the salty medicine frequently is conniving unknowingly at a medical crime It has been said that a physician s skill in managing the nervous patient may be judged by the amount of bromide that he prescribes Since bro

mides alleviate temporarily the symptoms which they produce they are habit forming and their sale should be regulated by law

Patients react with the widest possible variations to the presence of bromide in the body The mental symptoms range from a mild clouding of consciousness to active delirium and from slight depression to stupor and coma Attempts have been made to correlate the amount of bromide in the blood with clinical manifestations but individual susceptibility and associated disease make it impossible to do this with accuracy The studies in the literature have concerned themselves with the severer manifestations of bromide poisoning It is true that as a general rule greatly disturbed mental states seldom appear until the blood bromide concentration reaches 150 mgm per cent or more but Hanes and Yates in their analysis of 400 instances of bromide poisoning found that patients showing less than 150 mgm per cent of blood bromide frequently presented more or less striking evidence of intoxication

Such patients complain of dull morning headache constipation indigestion fatigue irritability sleeplessness difficulty in concentrating and poor memory The hands may be slightly tremulous and the gait a little unsteady at times due to dizziness Careful questioning of relatives may reveal that the patient has had brief periods of confusion and slight disorientation The picture is one of a mild neurosis and the usual therapy is bromide sedation It is the failure to recognize these milder manifestations of bromide poisoning that leads so frequently to severe intoxication

Craven[3] has given a very clear picture of the clinical manifestations of severe bromide poisoning as observed in this clinic An individual with one or a variety of medical or surgical complaints has taken bromides during a period of days or weeks After a variable length of time the patient becomes restless irritable and emotionally labile and complains of headache blurring of vision interrupted sleep and disordered usually frightening dreams As these symptoms endure there are observed weakness ataxia slurring and hesitancy of speech irrelevant conversation poor appetite and loss of memory particularly for recent events Drowsiness and lethargy soon are followed by stupor and sleep is even more disturbed by disordered dreams Hallucinations both visual and auditory become a prominent feature and maniacal attacks of excitement are provoked by the fear reaction produced

The chief symptoms and signs recorded in the histories of four hundred instances of bromidism[5] were in the order of their frequency, as follows (1) headache (2) irritability (3) emotional instability (4) weakness (5) lethargy (6) slurring speech (7) irrelevant speech (8) delusions

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6 grams of bromide daily in a proprietary medicine for the control of great restlessness and excitement

It is a common observation that the physician who is keenly aware of the possibility of the occurrence of a disease soon finds himself with a much larger experience of it than do his colleagues who are less sensitized to its manifestations Even when one is keenly alert to the possibility of bromide poisoning however it cannot be diagnosed with certainty by clinical means alone bromide must be demonstrated quantitatively in the blood for an exact diagnosis Fortunately an extremely simple and rapid qualitative urine test exists which gives reliable information as to the need for a quantitative blood bromide determination We are indebted to Otto Wuth[7] for the development and clinical application of simple and reliable urine and blood tests for bromide

Tests for Bromide in Urine and Blood

A *qualitative* test for bromide in the urine can be done very quickly and should be a routine test on neuropsychiatric patients The technic is as follows Clarify the urine to water clearness by shaking 15 c c with a half teaspoonful of powdered charcoal and filtering through fine filter paper To 5 c c. of this filtrate add 1 c c of 20 per cent trichloracetic acid and 1 c c of 0 5 per cent gold chloride solution (These reagents are furnished with the Wuth Comparator) A brown color is indicative of bromide This test should be controlled by one on normal urine known to be bromide free

The method for the *quantitative* determination of bromides in blood and spinal fluid used in Duke Hospital is a modification of Wuth's[7] and Katzenelbogen and Czorski's[11] methods * The procedure is as follows To 3 c c of oxalated blood (or spinal fluid) add 3 c c of water and 6 c c of 20 per cent trichloracetic acid Shake Allow to stand about 30 minutes and filter To 4 c c of the clear uncolored filtrate add 0 8 c c of 0 5 per cent gold chloride solution At the same time prepare a control made by adding 0 8 c c of 0 5 per cent gold chloride solution to 4 c c of a 10 per cent solution of trichloracetic acid If the color of the unknown is darker than the control indicating the presence of bromide immediately prepare a suitable standard as described in the next paragraph in the same manner that the unknown and control were prepared and compare in a colorimeter setting the standard at 20 mm

* This method is for use in chemical laboratories only For the practicing physician Wuth has devised an inexpensive and quite satisfactory colorimeter known as the Wuth Comparator which is manufactured by the LaMotte Chemical Co of Baltimore Md

(9) disorientation (10) hallucinations (11) loss of memory (12) cyanosis (13) vacuous facies (14) dilated pupils (15) stupor, (16) blurred vision (17) fabrication (18) ataxia (19) mental confusion (20) disordered dreams (21) vertigo (22) loss of libido and potentia

A rash was noted in only one fourth of the patients This usually was simple acne of the face and upper trunk though now and then papular or papulopustular in type The skin manifestations are no index of the severity of the intoxication Of 64 patients with 200 or more mgm per cent of bromide in the blood only 18 (28 per cent) had any rash whatsoever and in no instance was the rash characteristic enough to aid in diagnosis It would probably be a service to internal medicine if all references to bromide rashes were deleted from the text books *Skin manifestations are of very little or no value in the diagnosis of bromide poisoning*

Diethelm[9] points out that the mental reactions to bromide poisoning usually follow the pattern of the patient s own type of personality Certainly it is true that severe bromide poisoning may appear under the guise of any type of neurosis or psychosis Indeed the clinical evidences of bromide intoxication are so varied and so lacking in pathognomonic characteristics that there is only one safe rule to follow namely that a bromide test be done routinely on neuropsychiatric patients In the Duke Hospital Clinic we have found the information thus obtained quite comparable in value to that furnished by routine Wassermann and Kline tests It has been an absolutely indispensable aid in the diagnosis of a most puzzling group of cases frequently throwing a welcome light on a very obscure problem The physician rarely is able to exercise those God like attributes with which the laity is prone to endow him but when with confidence he can assure a sorrowing family that their distraught mother will emerge surely from her delirium within a few days he approaches very near to the public s ideal If he is wise however he will restrain his optimism until the patient s mask of bromide poisoning has been removed thus revealing conditions which may have been concealed

Diagnosis

Bromide intoxication should be suspected in every neuropsychiatric disorder if gross errors in diagnosis are to be avoided Clinical symptoms and signs of intoxication are very numerous and may appear in any order, in any combination and in any intensity Mild intoxications frequently are treated with bromides for nervousness Craven[10] has reported an instructive instance of a patient who was in a state of alternate coma and delirium for four months having been given by the family 4 to

fraction of the total halide or replacement is found as follows The sodium bromide concentration determined as above in mgm per cent is multiplied by the conversion factor 0 568 which is derived as follows

$$\frac{\text{molecular wt of NaCl}}{\text{molecular wt of NaBr}} = \frac{58\ 5}{102\ 9} = 0\ 568$$

This value divided by the mgm per cent of total halide gives the percentage replacement of sodium chloride by sodium bromide for example

Total Halides (Chloride and Bromide)	480 mgm per cent
Sodium Bromide	100 mgm per cent (as NaBr) or
	57 mgm per cent (100 × 0 568) as NaCl
Replacement of NaCl by NaBr	$\frac{57}{480}$ = 11 9 per cent

The statement is found not infrequently in the literature[4] that a replacement of more than 40 per cent of blood chloride by bromide is fatal The experience of the Duke Hospital Clinic does not confirm this Patients showing more than 40 per cent replacement are by no means rare The highest figure we have encountered is 48 per cent replacement and we have observed no fatality that could be ascribed to bromide poisoning

Treatment

The indications for treatment are clear and direct The offending bromide must be removed from the body and this is accomplished readily by the administration of sodium chloride In the Duke Hospital Clinic we administer considerably larger amounts of salt than are recommended in the literature It is said that chloride in large amounts mobilizes bromide in the blood too rapidly and thus may intensify the symptoms of intoxication We think that this is a theoretical danger which is overbalanced by the shortened hospitalization under vigorous treatment and a more rapid return of the patient when possible to a status of economic usefulness Depending upon the age and physical condition of the patient one may give from 6 to 12 grams of sodium chloride daily in addition to the salt present in the diet

Sodium chloride may be administered in several ways (1) *Intravenously* This is not the method of choice and should be used only when oral administration is too difficult or uncertain (2) *Rectally* This too is a method to be used only in the presence of difficulties in oral adminis

Preparation of Standard Bromide Solutions — A standard stock solution is made which contains 625 mgm of sodium bromide (Merck's Reagent) in 100 c c of distilled water Four working standards of different concentrations are prepared by diluting the stock solution as follows To 1 c c of stock bromide solution in a 100 c c volumetric flask add 5 5 c c of 2 per cent sodium chloride and 90 c c of 10 per cent trichloracetic acid Make up the volume to 100 c c with distilled water Four c c of this solution will contain 0 25 mgm sodium bromide The other standard solutions are prepared in the same way using 2 3 and 4 c c of the stock sodium bromide solution Four c c of these solutions then contain 0 5 0 75 and 1 0 mgm of sodium bromide respectively The sodium chloride is added to the standard solutions to approximate the amount found in the average blood filtrate By so doing a much better comparison of color between the unknown and standard can be obtained

The mgm per cent of sodium bromide in the unknown may be calculated by the use of the following formula

$$C_1 = \frac{R_2}{R_1} \times \frac{D_1}{D} \times C_2 \times \frac{100}{V}$$

where

C_1 is the mgm per cent of sodium bromide in the unknown solution

C_2 the concentration of the standard solution,

R_2 the reading of the standard solution in the colorimeter

R_1 the reading of the unknown solution in the colorimeter,

D_1 the volume to which the blood filtrate was diluted

D *the volume of the standard solution*

V the actual volume of the unknown (aliquot of blood taken for analysis diluted to D_1)

For example

$$C_1 = \frac{20}{R_1} \times \frac{4\ 8}{4\ 8} \times 0\ 25 \text{ (or } 0\ 5 \text{ or } 1\ 0) \times \frac{100}{1 \text{ c c}}$$

It has been mentioned above that when bromides enter the blood they not merely are added to the normal chloride concentration but actually replace chlorides which normally are excreted more readily by the kidneys than are bromides The *replacement* value then represents the percentage of total chloride of the blood which has been replaced by sodium bromide The total halide (chloride and bromide) is determined by the Whitehorn[1] method (precipitation of sodium bromide and sodium chloride with silver nitrate and back titration with ammonium thiocyanate) and is expressed as milligrams per cent of sodium chloride The bromide

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tration (3) *Orally* Most patients can be induced to ingest sufficient salt by mouth, and this is the best method of administration where it can be employed

Salt often is given in one gram capsules but in addition to the dis comfort of swallowing from 6 to 12 such capsules daily concentrated salt solutions are sometimes highly irritating producing nausea and vomiting A much superior method is to introduce the salt in bouillon One bouillon cube (Swifts weighing 3 gm) contains approximately 2 4 gm of sodium chloride hence 3 to 4 cups of bouillon daily provides adequate therapy Salt also may be given in enteric coated pills and as iced saline solution either plain or flavored

Bromide may appear in the gastric juice in concentrations greater than that of the blood indicating an active secretion of hydrobromic acid by the gastric mucosa In severe bromide poisoning continuous aspiration of the gastric juice (Wangensteen technic) aids materially in removing the deleterious bromine ions from the body

Few conditions respond more satisfactorily to adequate therapy than does bromide intoxication Improvement usually occurs within a few days and even the severest manifestations may disappear in from 7 days to 2 weeks[5, 8] The maniacal delirium frequently terminates quite sud denly the patient falling into a sleep from which he awakens relatively clear mentally It is common for minor relapses into disorientation to occur for short periods and the frightening dreams may persist for a week or more It is not possible to say with certainty in any given case at what bromide level symptoms will disappear

The usual sedatives are quite useless in controlling the delirium of bromide intoxication and they may even add to the excitement Paralde hyde may be used orally or intravenously but the result often is un satisfactory Restlessness may be alleviated by means of continuous tepid baths or wet packs

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CHAPTER XIX-I

POISONOUS REPTILES

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Introduction

The problem of snake venenation is not one that daily confronts the average physician yet there is hardly any considerable area in the United States or Europe where poisonous snakes do not occur while in tropical America Asia Africa and Australia many species of this group of reptiles are hazardous to the life of man and domestic animals In contrast to the relatively low incidence of snake bite is the high mortality due primarily to the ignorance of the public and of physicians concerning the proper management of snake poisoning

The ancients were familiar with many kinds of snakes which the Greeks referred to as *echis* and *colubra* but these terms were not limited by them to the generic concepts which are implied today The Hindus Persians and Eastern

Mediterranean peoples became acquainted with the cardinal symptoms of snake poisoning and developed many methods of treatment The majority of these were based on alchemy and religious incantations, but experience demonstrated the value of ligature above an affected limb, scarification and cupping of the wound and the administration of stimulants, practical measures which are useful as first aid in present-day medicine Among the many contributions to medicine made by the Italian physiologist Francesco Redi was his inquiry into viper poisoning and his discovery (1664)[1] that the blood of animals which were experimentally bitten frequently coagulated He concluded that death due to the ' bite" of the snake resulted from this coagulation The next important study was a chemical analysis of viper venom made by Prince Lucien Bonaparte (1843) who found that it resembled albumin S Weir Mitchell (1860)[3] Mitchell and Reichert (1886)[4] and Martin (1896)[5] demonstrated that the effective principle of venom is toxalbumin

Modern knowledge of the toxins in snake venom is based on the classical studies of Flexner and Noguchi (1902)[6], Lamb and Hunter (1904–1907)[7] Elliot (1904)[8] and Calmette (1908)[9] These workers discovered that many snake venoms contain hemolysins cytolysins hemorrhagins coagulins anti-coagulins and neurotoxins, while the potency of others is limited essentially to neurotoxic substances In the vipers the hemotoxin is almost always the important fraction while in the cobras and their kin the neurotoxic fraction predominates These observations have lead to the development of specific univalent and polyvalent antivenins in various parts of the world

Etiology

Vertebrate animals which are harmful to man by virtue of poisons or venoms that they elaborate include fishes lizards and snakes Certain salt water fishes are poisonous as food particularly during the spawning season Their flesh contains a thermostable neurotoxin and an intestinal irritant Examples are the jack fishes (madregal cavalla or jurel) the kingfish (sierra or pintado) the barracuda and the red snapper Other fishes, including the more primitive cartilaginous types (elasmobranchs) as the stinger rays and some of the bony fishes (teleosts) have poison filled barbs connected with the dorsal or anal fins or situated under the opercular spines Although some of these fishes are harmless unless the barbs are accidentally broken, many more have patent barbs which inject poison into any wound made by the barb Both local inflammation at the site of the injection and neurotoxic symptoms are frequently recorded A third group of fishes, represented by several species of eels belonging to the genus *Muraena* envenom their victim by their bite These fishes have poison glands in the roof of the mouth and secrete their product between powerful sharp ungrooved palatine

teeth The person who is bitten experiences painful local swelling at the site of the bite and a feeling of suffocation at times with syncope

The *Reptilia* which are venomous are the *Lacertilia* or lizards, Gila monsters belonging to the genus *Heloderma*, and many species of *Ophidia* or snakes The Gila 'monsters' possess four conspicuous limbs and a relatively short tail like a crocodile or alligator They will be considered at the end of this chapter

Snakes

These reptiles are elongated and limbless have a horny covering of epidermal scales possess a very flexible mouth a forked tongue which frequently is projected from the closed mouth lack eyelids are provided with an external auditory meatus and have a transverse cloacal opening and a paired penis The unique distensibility of the mouth so that the jaws may at times be separated by 180° from one another is due to (a) the mobility of the quadrate bone (b) the loose attachment of the maxillary bone and (c) the elastic symphysis which joins the two mandibles Locomotion in snakes is accomplished by the flexibility of the vertebral column and the mobility of the very large number of curved wire like ribs

All snakes have poison glands The majority of species have unspecialized palatine secretions like the eel *Muraena* Others have special fangs through which venom passes into a wound at the time the snake strikes the victim Zoologists recognize approximately 2 400 species of snakes which are separated into the following nine families

1 *TYPHLOPIDAE* (Blind Snakes) — Small burrowing in the moist soil of warm climates possess no ventral shields provided with two to three pairs of unspecialized maxillary teeth *harmless to man*
2 *GLAUCONIIDAE* — Tropical forms somewhat resembling the Blind Snakes in appearance but lacking maxillary teeth *harmless*
3 *BOIIDAE* (Boa Constrictors and Pythons) — Tropical forms which are large (up to 30 feet in length) and powerful with vestiges of pelvis and femora ventral shield not extending to flanks (i e not visible from lateral aspect) *non venomous but may crush or strangle victim*
4 *ILYSIIDAE* — Small tropical box like forms with narrow ventral shields one species may be mistaken for poisonous coral snake *harmless*
5 *UROPELTIDAE* (Peg tails) — Small burrowing forms with stumpy or truncated tails restricted in distribution to South India and Ceylon *harmless*
6 *XENOPELTIDAE* — Only one species found in Southeastern Asia provided with premaxillary teeth, at times mistaken for terrestrial Colubridae *harmless to man*

—

7 *AMBLYCEPHALIDAE* — Insectivorous forms resembling the Colubridae occurring in Tropical America and Southeastern Asia *harmless*

8 *COLUBRIDAE* — With very broad ventral plates which are visible laterally head covered with large symmetrically arranged scales possess several maxillary teeth more than 1 300 species distributed throughout the world except in cold climates and in a few small areas in the Indo-Pacific region

This family is divided into three sections

Section I *AGLYPHA* (without true fangs) — Provided with unspecialized maxillary teeth but lacking grooved teeth or fangs for injecting saliva into victim, more than 700 species mostly terrestrial but some are aquatic and a few are marine *harmless to man* (See Fig 1A)

Section II *OPISTHOGLYPHA* (with one functional fang at the posterior end of each of the two long maxillae about 300 species, well distributed throughout the world, potentially venomous but *usually harmless to man* and large animals because of the position of the fangs (See Fig 1B)

Section III *PROTEROGLYPHA* (with one functional fang arising from each of the two antero-posteriorly compressed maxillae) about 200 species of which several are *very harmful to man* This Section is divided into two subfamilies

Subfamily *HYDROPHIINAE* (Sea Snakes) — With tail strongly blade like or paddle like in the sagittal plane 60 or more tropical marine species occurring mostly in relatively shallow water near shore possess *very virulent venom*

Subfamily *ELAPINAE* — Land snakes with cylindrical tail contains *some of the most venomous snakes* (See Fig 1C)

9 *VIPERIDAE* — All species lack unspecialized maxillary teeth but possess a single large tubular canalized fang ankylosed to each of the two short anteriorly-disposed maxillae entire group of a few hundred species technically referred to as *SOLENOGLYPHA* (i e, possessing a single fang) *all species venomous* This family is divided into two subfamilies

Subfamily *VIPERINAE* (True Vipers) — Lacking a sensory pit between the eye and nostril widely distributed throughout Europe Africa and Asia not found in America or Australia

Subfamily *CROTALINAE* (Pit Vipers) — With a conspicuous sensory pit between the eye and nostril head more or less distinctly broad in the occipital region hog nosed anteriorly with American and Asiatic distribution (See Fig 1D)

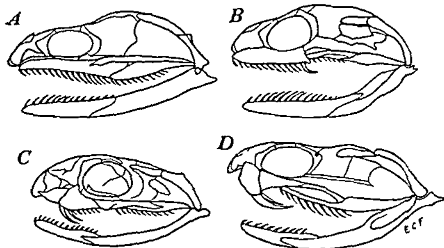


Fig 1 Skeletons of the head of non venomous and venomous types of snakes A *Aglypha* (i e without fangs) non poisonous B *Opisthoglypha* (i e with posterior fangs) usually harmless to man C *Proteroglypha* (i e with front fangs) including cobras kraits mambas true coral snakes Australian poisonous snakes and sea snakes D *Solenoglypha* (i e with single fangs) including true vipers as well as the rattlesnakes copper head water moccasin and other pit vipers Original adaptations

An examination of the classification of snakes which has just been presented indicates that those which are harmful to man are (1) the family of boa constrictors and pythons which are physically dangerous (2) the proteroglyph colubrids including the sea snakes true coral snakes cobras kraits mambas and Australian species and (3) the entire family of vipers Both of these latter groups consist of species which are capable of inserting their fangs into the skin of man and injecting lethal amounts of venom

The Venom Apparatus (Fig 2) — This consists of a pair of venom glands and associated structures the gland ducts and two functional fangs There is a single almond shaped racemose venom gland on each side of the head at the angle of the jaw it is homologous to the parotid gland of mammals Internally the gland consists of a central cavity into which numerous small ducts open These branch many times as they proceed peripherally to a multitude of minute blind alveoli just within the wall of the gland they are supported by a framework of fibrous tissue In some colubrids and in all vipers the size of the venom gland is responsible for the enlargement and widening of the head posteriorly A few colubrid snakes and one viperine species have long venom glands which extend back into the neck The venom elaborated in the gland is passed forward through a capillary duct which makes an upward curve under the plane of the eyes and then

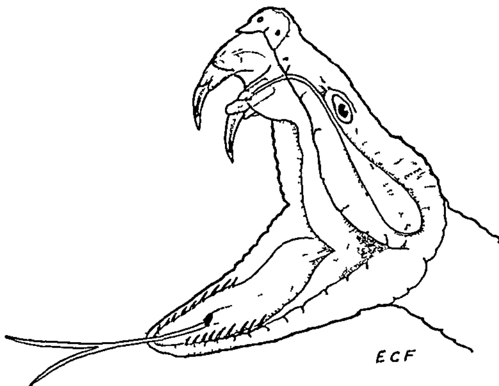


FIG 2 Head of a pit viper such as a rattlesnake with mouth open and fang erect ready to strike The position of the venom gland with its capsule and ligamentous attachments and the venom gland duct are indicated. Original

makes an abrupt downward bend to the base of the fang The venom is passed down the canal of the fang to be discharged through an orifice near its tip

A capsule made up of two layers of tough semi-elastic, fibrous tissue surrounds the venom gland The outer layer is continued posteriorly as a ligamentous ribbon, which has its point of insertion at the junction of the mandible and internal pterygoid bone A short ligament attaches the gland medially to the skull while a third ligament is connected with the external pterygoid muscle In venomous snakes contraction of the middle and posterior temporal muscles serves to close the mouth while contraction of the anterior temporal muscle which has its origin in the upper portion of the gland capsule and its insertion upon the mandible produces a powerful squeezing effect on the venom gland comparable to that caused by the closing of a hand around a rubber syringe bulb

The mechanism of the ' strike inaccurately referred to as the 'bite , differs considerably in the cobra representing the proteroglyphs and the rattler representing the solenoglyphs In the cobra the slightly back curved fang is relatively short in most species and is immobile due to the fixed position of the maxilla The lower jaw is used to assist the fang in piercing the skin of the victim, after

which deeper penetration is effected by a chewing movement In the rattlesnake the curved fang is relatively long Due to the extreme mobility of the maxilla to which it is firmly ankylosed when it is not in action it lies back against the anterior roof of the mouth effectively covered by a membrane the vagina dentis When action is initiated the maxilla and fang revolve forward so that the fang is in an erect effective striking position There is no need for the lower jaw to assist in the strike Amaral (1945)[10] refers to the strike of a rattler as a ' stab In vipers the greater mobility of the quadrate bone allows a considerably wider opening of the mouth than in proteroglyphs

In both groups the strike usually consists of four separate movements (1) the snake prepares for the strike by raising its neck in an S shaped or inverted question mark loop while the posterior part of the body remains coiled on the ground for leverage (2) the mouth is opened and the fangs are erected (3) the strike occurs and venom is injected (4) the fangs then are retracted

Envenenation serves two purposes for the snake It aids materially in killing or at least paralyzing its prey such as rodents lizards frogs and toads birds and other snakes It kills or temporarily incapacitates its enemies including large animals which could not be otherwise dealt with

The Venom —This is a clear viscous, slightly yellowish colored liquid which is acid in reaction and is thermolabile Its toxic properties are destroyed by gastric and pancreatic juices silver nitrate NaOH KOH formaldehyde alcohol and by ultra violet radiation It is readily soluble in water but is insoluble in alcohol or ether On dehydration the venom is lemon or orange yellow in color and will remain potent for years at ordinary room temperatures Its specific gravity varies for different species (rattlesnakes 1 030 to 1 044 cobras 1 11 Russell s viper 1 077) Crude venom contains albumin and globulin proteoses and peptones mucin and mucin like fractions ferments fats calcium chloride calcium phosphate magnesium phosphate and ammonium phosphate as well as cellular detritus and contaminating micro-organisms (Amaral 1945)[10] The effective principle is a complex of toxalbumins

The yield of venom varies greatly in different species of snakes and in different sizes of the same species A few examples in milligrams of dry venom may be cited to illustrate this point

North American species

Copperhead (*Agkistrodon mokasen*) full grown		45–60
Water moccasin (*A piscivorus*) full grown		90–150
Eastern diamond back rattler (*Crotalus adamanteus*) full grown		240–864
Western diamond back rattler (*C cinereus* or *C atrox*) full grown		90–160
2 ft 11 inches	5 3	
3 ft 7 inches	11 5	
4 ft 4 inches	21 8	
5 ft	40 0	
6 ft	50 0	

Timber rattler (*C horridus*) full grown	60–90
Prairie rattler (*C viridis*) full grown	60–75
Massasauga or pigmy rattler (*Sistrurus catenatus*) full grown	5 5–6 0
Coral snake (*Micrurus fulvius*) full grown	only few mgm
Central American species	
Cascabél (*Crotalus terrificus*) full grown	30–60
Fer-de lance (*Bothrops atrox*) full grown	80–160
Bushmaster (*Lachesis muta*) full grown	300–500
Indian species	
Indian cobra (*Naja naja*) full grown	250–300
Daboia or Russell s viper (*Vipera russelli*) full grown	00–300
African species	
Mamba (*Dendraspis angusticeps*) full grown	50–80
Carpet viper (*Echis carinata*) full grown	18 8
Australian species	
Copperhead (*Denisonia superba*) full grown	20–35 6
Death adder (*Acanthropis antarcticus*) full grown	60–85
Tiger snake (*Notechis scutatus*) full grown	30–50
Black snake (*Pseudechis porphyriacus*)	47 2

Distribution and Bionomics of Poisonous Snakes

North America — The species of poisonous snakes in North America consists of two venomous corals (Proteroglypha subfamily Elapinae) and the group of the pit vipers (Solenoglypha subfamily Crotalinae)

The venomous *coral snakes* have a slender cylindrical body with brilliant broad bands of coral red and coal black separated by bands of golden yellow, and a solid black snout False coral snakes which are non poisonous have pink or yellowish noses The head of true coral snakes has the same width as the neck The harlequin coral snake *Micrurus fulvius* is widely although rather sparsely distributed throughout the Southeastern United States from North Carolina to Florida and westward through southern Louisiana and the Gulf Coast of Texas to the Rio Grande It lives among decaying leaves and moist humus and usually feeds on small snakes and lizards It reaches a maximum length of 36 to 40 inches The Sonoran coral snake *M euryxanthus*, has a more westerly distribution from western Colorado and Utah southwestward to Mexico and the southern part of California It lives on relatively dry ground and feeds on snakes and lizards It seldom exceeds 36 inches in length These snakes are quiet and do not attack man unless they are provoked but they may attack suddenly, and because the wound is slight it may be neglected and prove fatal

The *pit vipers* in the United States include the copperhead *Agkistrodon mokasen* the cotton mouth moccasin, *A piscivorus* the small rattlers massasauga and the pigmy rattler and a dozen or more true rattlers belonging to the genus *Crotalus* The body of these species is rather broad, somewhat flattened dorsoventrally, and the head is broader than the neck

The *copperhead* (highland moccasin) has an extensive distribution from the Eastern into the South Central United States (see map Fig 3) from southern New Hampshire to northern Florida and central Illinois into eastern Kansas eastern Oklahoma, northern Louisiana and south central Texas It prefers hilly or rocky places but may invade gardens in search of small rodents toads frogs and small birds which are its food Because of its close proximity to human communities its vicious habits and sudden striking movement it produces considerably more than half of the snake bites in this highland area This species is of medium size with a maximum length of about four feet The *water moccasin* or *cotton mouth moccasin* so-named because of its pinkish white buccal mucosa is a lowland species which inhabits the swampy places in the Southeastern United States from Virginia to the Rio Grande but with extensions of territory up the Mississippi valley to lower Illinois and from Mobile Bay up into Kentucky (see map Fig 3) It feeds on fish frogs aquatic reptiles and rodents It strikes promiscuously and is responsible for many of the bites throughout its range This species is moderately large with a maximum length of about six feet

The *massasauga Sistrurus catenelus* has a northeastern race which occurs from western New York through southern Ontario and southern Michigan to Kansas and a southwestern race which extends from western Kansas through Oklahoma western Texas and New Mexico to southeastern Arizona and adjacent Mexico It is found both in prairie and swamp land and feeds on small rodents frogs and toads Its tail is provided with rattles and the head is covered with shields This is a rather small species which attains a maximum length of about 42 inches The *pigmy* or *ground rattler S miliarius* has approximately the same area distribution as the water moccasin (see map Fig 3) However it prefers drier ground finding its food small rodents among dry grass and leaves It is a very small snake only 20 inches long and secretes very little venom Yet from time to time it strikes human beings especially small children

The *timber rattler Crotalus horridus* also referred to as the black rattler banded rattler or cane breaker has an extensive distribution from New England to Georgia and into the plains states It is primarily a highland species living among rocks and in crevices of wooded or hilly regions where it feeds on rodents and birds It is shy is not readily irritated and unless provoked does not often attack man It reaches a maximum length of about five feet Like other species of *Crotalus* its head is covered with scales

The *Eastern diamond back rattler C adamanteus* has a range from North Carolina to Florida and westward to Louisiana (see map Fig 3) It lives in swampy regions but not in the swamps themselves and feeds primarily on rodents and quail This is perhaps the most excitable as well as the largest venomous snake in North America (7 to 8½ feet maximum length) It secretes a large amount of venom and produces a very severe wound with extensive sloughing Its western

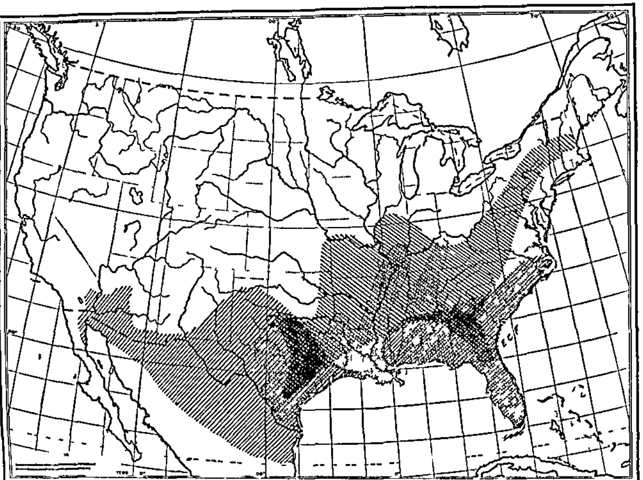


Fig 3 Map showing the distribution of the four most common poisonous snakes in the eastern and southern United States ▨ = Eastern diamond back rattler (*Crotalus adamanteus*) and Western diamond back rattler (*C atrox* or *C cinereus*) ▨ = copperhead (*Agkistrodon mokasen*) ▨ = water moccasin or cotton mouth (*A piscivorus*) Original

counterpart *C cinereus* or *C atrox* has a distribution from southwestern Louisiana to the southern tip of California and the northern states of Mexico (see map Fig 3) It is found in dry rocky regions as well as on cultivated land where it catches rodents for food It is very excitable its bite is highly venenating and the mortality rate is considerable This species reaches a maximum length of about 7 feet

The *true prairie rattler C viridis* or *C confluentus* has a wide range through the plains states from Canada to Mexico and to the Pacific Coast Different races inhabit prairie and mountainous areas Its food consists of various species of rodents Its bite is somewhat less severe than that of the diamond backs It reaches a maximum length of about 5 feet

Other species of rattlers which occur in North America include the *red rattler C ruber* of southern California which lives in rocky deserts and feeds on rodents the *Mojave rattler C scutulatus* of the southwest desert regions the *black tailed rattler C molussus* of the southwestern states and northern Mexican highlands the *sidewinder* or *horned rattler C cerastes* of the Western States which feeds on lizards and rodents the *tiger rattler C tigris* with a range from southern Nevada and California into Mexico and a preference for rodents as food the *green rattler C lepidus* with a highland distribution from western Texas through southern New Mexico and Arizona to Mexico the *spotted rattler C triseriatus* which extends from the mountains of southern Arizona into Central Mexico and *Willard s rattler C willardi* known only from New Mexico and southeastern Arizona To the south of the United States there is the large venomous neotropical rattler which has an extensive distribution southward through Latin America Several other species have been described for the Western States

Latin America — In addition to several species of venomous *coral snakes* which have habitats and habits not unlike the harlequin and Sonoran coral snakes of North America there is an abundant fauna of pit vipers and one dangerous sea snake These include the *tropical rattler* or *cascabél Crotalus terrificus* with a distribution from Mexico to Brazil and a maximum length of seven feet It is much less nervous but more aggressive than North American rattlers frequently does not give warning with its rattles is highly venomous and has a preponderance of neurotoxins over hemotoxins It is found principally in hilly or mountainous country Other neotropical rattlers are small sized or of limited distribution

In Mexico and Central America one finds the *cantil Agkistrodon bilineatus* the counterpart of the water moccasin It is smaller in size less than four feet long is semi aquatic and is encountered rather infrequently However its venom is highly toxic The *bushmaster* or *cascabela muda Lachesis mutus* is as its name implies the master of the bush and extends from Nicaragua to Southern Brazil and on the island of Trinidad It reaches a maximum length of more than eleven feet is very aggressive and makes a vibrating buzz with its tail Moreover

it has the longest, most powerful fangs of all venomous snakes and injects a large amount of potent venom deeply into the flesh It lives in damp, wooded, but not necessarily swampy areas Unlike all other pit vipers the bushmaster lays eggs instead of giving birth to living young

The majority of the neotropical pit vipers belong to the genus *Bothrops*, including the formidable *fer de lance* or *barba amarilla* *B atrox*, which reaches a length of more than eight feet and has a range extending from southern Mexico to northern South America and some of the West Indies, the small *palm vipers*, *B bicolor* *B schlegelii*, which have prehensile tails and are concealed in the foliage of trees in the moist lowland from Mexico to South America, the *jumping viper*, *B nummifer*, about three feet in length of relatively low toxicity and having a range from Mexico through Central America, the *hog nosed vipers* or *tamagás* *B nasuta*, *B lansbergii* and *B ophryomegas* small sized aggressive species with a range from southern Mexico to northern South America, *Maximilian's viper* or *jararáca*, *B neuwiedii* a small but highly venomous fer-de lance type of Brazil and the handsome *urutu* *B alternatus* which lives in parts of Brazil, Paraguay, Uruguay and northern Argentina

The *yellow-bellied sea snake* *Pelamydrus platurus* which is recognized readily by its laterally compressed rudder like tail is the only species of the *Hydrophinae* in the Western Hemisphere It is found in relatively shallow waters along the Pacific Coast of Costa Rica and Panama Although it has potent venom, accidental human contact with this snake is infrequent

Palearctic Region — In *Europe* and *Northern Asia* the only poisonous snakes are the *true vipers*, all belonging to the genus *Vipera* These with their geographical ranges are as follows The *common viper* *V berus* from Great Britain throughout Europe to the Amur River and Saghalin Island Maritime Provinces U S S R *Orsini's viper*, *V ursini* Southern Europe *Renard s viper* *V renardi* southern Russia to Central Asia, *asp viper* *V aspis* dry mountainous regions of southern Europe *Lataste s viper* *V latasti* stony forested areas of Spain Portugal Morocco and Algeria *sand viper* *V ammodytes* Austria and Balkans and *blunt nosed viper* *V lebetina* Mediterranean coastal area The majority of these snakes do not exceed two feet in length, but the blunt nosed species may reach four to five feet Their food varies from small mammals, birds and lizards to grasshoppers The sand viper has the most potent venom and frequently causes death of its victims

Asia — In southern Asia (*Oriental Region*) there are many species of poisonous snakes which include cobras and kraits true vipers pit vipers coral snakes and the sea snakes

The *Indian* or *spectacled cobra* *Naja naja* is the most notorious and one of the most prevalent snakes throughout southern Asia from India to the China Sea It is relatively slender and has a small head but is able to inflate its neck region

by moving its anterior ribs forward under the loose skin thus producing a characteristic hooded appearance Its coloring is yellowish to dark brown frequently with black and white spectacled spots on the hood It reaches a length of 6 feet This snake is very excitable and strikes with a forward arching of its neck holding on to the victim for some time while it injects its venom Many accidents occur inside native habitations which it enters in search of rats mice and frogs on which it feeds About 70 per cent of its venenation is fatal A related species the *king cobra* or *hamadryad* *N hannah* is the longest of all poisonous snakes reaching a maximum length of more than 18 feet Its color is olive or yellowish brown at times interrupted with black rings It is found in the region from eastern India to the Philippines and feeds almost exclusively on other snakes Although it has potent venom it seldom attacks man The *kraits* are relatively small snakes which grow to a maximum length of 4 feet They have a ridged backbone covered with broad scales There are several species with a distribution from India to Formosa They are fond of close association with human beings Although their venom contains potent neurotoxins they seldom attack man The two best known types are the *common krait* *Bungarus candidus* and the *banded krait* *B fasciatus*

The *true vipers* of Asia are represented by *Russell s viper* or *daboia* *Vipera russelli* which reaches a length of five feet hisses is very dangerous and is distributed from Cyprus and Asia Minor through India to Siam the small 20 to 24 inch deadly *saw viper* *efa* or *phoosa* *Echis carinata* occurring from Syria to India and its relative *E coloratus* known from Palestine and Arabia the *horned viper* *Cerastes cornuta* extending from Southwestern Asia to India and species of *Azemiops* 2½ feet long Burma hills as well as *Pseudocerastes* in Persia and Baluchistan

Africa — The continent of Africa has as large an array of poisonous snakes as does the oriental region These include both proteroglyph and solenoglyph species Among the former are several species of cobras the mambas the spitting snake and members of four other genera Among the latter are vipers puff adders and representatives of five other genera

The *black necked cobra* *Naja nigricollis* has an extensive distribution ranging from Southern Egypt to Angola and the Transvaal It is a powerful snake of large size with a maximum length of seven feet and a head elevation of three feet from the ground On slightest provocation it sprays its venom forward and upward to a distance of twelve feet and by temporarily blinding its victim overpowers it The *Egyptian cobra* or *asp* *N haje* extends through North Africa and southward from Egypt to Natal This is the snake famed in Egyptian history It reaches a length of six feet does not spit venom but is very irritable hisses and strikes its victim repeatedly Other cobras of equally bad temper and aggressiveness are the *black cobra* *N melanoleuca* which is even larger than *N nigricollis*

and inhabits tropical Africa the *Cape cobra N flava* with a distribution from Tanganyika to the Cape of Good Hope, and three species occurring in West Africa The *aquatic cobra, Boulengerina stormsi*, frequents water courses in the Cameroons, the Congo and around Lake Tanganyika Although it grows to a length of eight feet, it is considerably less aggressive than the true cobras

The *mambas, Dendraspis* species, are slender, arboreal forms with greenish and blackish coloration which conceals their presence from their victims One species, *D angusticeps* reaches a length of twelve feet Although these snakes at first look harmless, they are most deadly The several species of mambas cover most of Africa south of the Sahara

The *ringhals* or *spitting snake, Haemachatus haemachatus*, is a small, thick dark colored member of the cobra group with light neck bands and a length of about four feet It is prevalent throughout South Africa but has also been recorded from the West and East When disturbed by a person stooping or kneeling nearby it advances on the individual and ejects its venom in two jets from its fangs this is transformed into a dangerous spray as the snake expels air from its lungs In contact with the eyes it causes intense pain and partial or total blindness The strike of this snake also is deadly

The African vipers have extensive distribution throughout the continent The *puff adder, Bitis arietans* which is ornamented beautifully by black chevrons separated by narrow yellow crescents on its back, is a massive creature reaching a length of five feet It inhabits the grasslands, rocky regions and lightly timbered areas near streams at low altitudes It is not particularly aggressive but when endangered, it strikes very rapidly The venom is highly toxic but acts slowly compared with cobra poison The *rhinoceros horned viper V nasicornis* is a semi aquatic species confined to the rain forest belt from the West Coast inland to Uganda and Kenya Colony It is stout multicolored and not more than four feet long Its name is derived from a pair of epidermal horns jutting out from its nose Although it hesitates to attack man its venom is potent The *Gaboon viper V gabonica*, has a body coloring of buff, brown, pink and lavender hues Its head is particularly broad At times it has a median nasal horn It reaches a length of nearly six feet Although this snake is not easily irritated its strike is particularly dangerous because of the very long fangs 2 inches in length and the large amount of neurotoxins in the venom comparable to cobra toxin This snake lives in dense jungles of West Africa Other species of vipers include the small *horned vipers B cornuta B caudalis* of sandy, semi-desert areas the *mountain adder B stropos* of South Africa the *sand viper Cerastes vipera* and the *carpet viper* of the Sahara, all of which have effective color adaptation and are highly venomous One additional viper the *night adder Causus rhombeatus*, which grows to about three feet in length and extends from the upper reaches of the Nile to South Africa hides in the daytime and prowls at night It frequently

enters human habitations in search of rodents Although it has long poison glands which extend well into the neck the venom is much less toxic than that of most of its relatives

One member of the *Opisthoglypha* or rear fanged snakes which at times venenates man and domestic animals is the *boomslang* or *tree snake Dispholidus typus* It is found in East and Southeast Africa is large up to six feet long powerful and displays a confusion of color patterns from grass-green through various shades of brown to all black Its mouth opens wide and if it can engage its fangs in the skin of an unsuspecting human victim it can inject a nearly fatal dose of venom (Loveridge 1928)[11]

The Western Pacific, South Pacific and Australia — Several of the poisonous snakes of the Indian region extend to South China French Indo-China Siam and Malaya but some additional species occur on the mainland and in the islands around the China Sea Examples of the latter are pit vipers belonging to *Agkistrodon* the moccasin group which occur in Japan near the China Coast and in Malaya and species of *Trimeresurus* arboreal and terrestrial forms which resemble the *Bothrops* group of the American Tropics These species extend from the Riu Kiu Islands south through Formosa into the Philippines

All of the poisonous snakes of Australia excluding the sea snakes belong to the proteroglyph subfamily Elapinae which especially elaborate neurotoxins Five species require mention because of their medical importance The large *black snake Pseudechis porphyriacus* which reaches a length of seven feet is widely distributed throughout the Continent except in the tropical north It is found primarily in and about streams and is a hazard to bathers The *copperhead* of southern Australia and Tasmania *Denisonia superba* is a somewhat stouter species than the black snake is slightly shorter frequents swamps and water courses and is more menacing and venomous The *brown snake Demansia textilis* with a small head slender build and a length of five to six feet is widely distributed Although it looks harmless its strike is highly dangerous since its venom is potent The *tiger snake Notechis scutatus* with dark brown banding and a length of five to six feet inhabits the dry lands of Australia and Tasmania It has venom more potent than that of any other known snake It becomes enraged on least provocation attacks its victim and within an hour may cause death It produces more fatalities than all other snakes in Australia The *death adder Acanthopis antarcticus* is a short stout form resembling a viper It occurs throughout most of Australia as well as in New Guinea and the Moluccas Many other snakes of related species are found in New Guinea and the Solomons while one elapine genus is reported for Fiji Most of the South Sea Islands and the Hawaiian Group are free of land snakes

Sea Snakes in the Indian and Pacific Oceans — Many species of sea snakes occur in the shallow waters a few hundred yards out from shore not far fror

river mouths They abound all the way from the Persian Gulf to Formosa along the north coast of Australia and in the waters of the Dutch East Indies and South Pacific Islands They seldom attack man except fishermen, who haul them in with their nets or divers who accidently contact them Their venom varies from the potency of the Indian cobra to relatively non toxic

For more detailed information on poisonous snakes of the Eastern Hemisphere the reader is referred to Phisalix (1922)[1] and for those of Australia to Fairley (1929)[13]

Epidemiology

The circumstances and methods whereby human beings are exposed to the venoms of poisonous snakes vary widely An Indian fakir or a caretaker of a serpentarium may have misjudged the apparent tameness or docility of cobras or adders or a religious fanatic may have tempted drowsy rattlers to strike Again, persons exhibiting snakes and fully aware of the dangers of their fangs may have pulled the functioning pair some weeks previously without realizing that a replacement pair had already become functional These individuals constitute a group with relatively high mortality from snake venenation, but they can not expect much sympathy

A larger and more diverse group of the population in areas where poisonous snakes are abundant, encounter them accidently in pursuit of daily work or during periods of recreation The workman may be engaged in weeding his garden and come in contact with an American copperhead snake or he may surprise a water moccasin in a cypress swamp or rice field or a diamond back rattler in an upland farm It may be in Central America, where a palm viper lurks in an overhanging bough or the dreaded bushmaster enters camp at night and is stepped on bare foot It may be a native in the African bush or a legionnaire in Tunisia who accidentally encounters a viper It may be a South Pacific native who has drawn in a sea snake with his haul of fish and in trying to separate it from his catch is struck by the snake Finally it may be a hunter in Africa who is sprayed with venom at a distance of several feet and become frenzied with blinding pain

The examples which are cited will illustrate the variety of situations which may provide exposure to snake venenation The actual danger of a strike depends in part on the irritability and aggressiveness of the particular species of snake in part on its ability to strike deeply into the flesh the amount and potency of its venom and the warning which the potential victim has of his danger Although there has been repeated demonstration that a new supply of venom i rapidly elaborated following exhaustive discharge of the normal complement in the venom glands there are periods when many venomous snakes are lethargic and are not easily provoked In the United States even along the Gulf Coast

the winter is usually a hibernating season Only when warm spring sunshine increases metabolism and the skin is shed does the animal become dangerous Moreover after the snake has secured and swallowed a sizeable meal and while this is being digested there is considerably less danger than when the reptile is in search of food However these examples should not engender a sense of false safety it is much wiser to be constantly on guard Finally most poisonous snakes are dangerous soon after birth

Some years ago Hutchinson (1929[14] 1930[15]) published reports collected by the *Antivenin Institute of America on 863* cases of snake poisoning in the United States for the years 1928 and 1929 In the order of frequency by different species of snakes these were as follows copperhead *Agkistrodon mokasen* 308 Western diamond back rattler *Crotalus cinereus* or *C atrox* 194 Western prairie rattler *C viridis C confluentus* or *C oreganus* 128 water moccasin 82 timber rattler *C horridus* 74 pigmy rattler *Sistrurus miliarius* 40 Eastern diamond back rattler *C adamanteus* 26 sidewinder *C cerastes* 7 massasauga *S catenatus* 4 Of the 40 deaths in this series 14 were due to *C cinereus* 9 to *C horridus* 8 to *C viridis* 5 to *A piscivorus* 3 to *C adamanteus* and one to *C cerastes* These data are only partial and do not include a probably larger number of persons *poisoned in rural areas which furnished no reports*

The copperhead is active from late April until mid November with the greatest number of strikes during the late summer the water moccasin from March to October but with one accident reported for January the pigmy rattler from late March until November the massasauga in early summer the timber rattler from early May to mid-October the Eastern diamond back scattered from late January to mid October the Western prairie rattler from April to October the Western diamond back practically throughout the entire year the sidewinder from April through September Less frequently there are cases of strikes from other rattlers and from coral snakes

In 1928 69 2 per cent of the victims were males and 50 per cent of all persons bitten were under 20 years of age In children under 5 years of age the sexes were about equal Parallel figures were reported for 1929 The circumstances under which the accidents occurred were reported also for 19 8 as follows stepping on too close to or falling near snake 120 at work 66 at play 64 reaching in or under a limb stone or other object 37 while fishing 19 while handling captive snake 19 while hunting 14 while swimming 8 picnicking 3 catching snakes 3 while asleep out-of-doors 1 picking up or lifting berries 34 pulling weeds or picking flowers etc 30 *picking up fallen fruit* 12 picking up wood 10 picking cotton 8 lifting stones 3 gathering peanuts 3 and searching for fish worms 1

As summarized from the 1928 and 1929 records referred to above in the order of frequency the parts of the body injured were foot 237 finger 213 shin 157

ankle 135 hand 126 forearm 39 wrist 18 thigh 8, head 8 upper arm and trunk each It is evident that the digital parts of the extremities are endangered most frequently due to stepping on or near a poisonous snake or to picking up objects with the unprotected hand

PATHOGENESIS AND PATHOLOGY

The type and degree of local and systemic damage produced by poisonous snakes depend on several conditioning factors The amount of the venom is as a rule dependent on the size of the snake Its ability to strike its victim in such a way as to sink the fangs well into the deeper layers of the skin also is very important Thus the back fanged snakes are not particularly dangerous to human beings unless like the boomslang they are large enough to compensate for their mechanical inefficiency In general, the viper family have a superior striking mechanism over the elapine species yet some cobras kraits and mambas are more deadly than certain vipers of like size Even small front fanged species are greatly to be feared because of the potency of their venom

Toxicologically snake venom consists of several fractions which vary in amount in different ophidians In most elapine species as cobras kraits asps mambas corals and Australian poisonous snakes as well as in the sea snakes and a few vipers like the neotropical rattlesnake and the Gaboon viper the principal venom is a neurotoxin which is combined with varying amounts of hemolysin anticoagulin and in some species thrombase In the viper family the principal constituents usually are hemorrhagin cytolysins and thrombase

According to Fairley (1929)[13] neurotoxin has a special affinity for the cells of the respiratory centre and the bulb, though it also involves nervous tissues elsewhere in the cord and brain The toxin attacks the ganglionic nuclei causes granular necrosis and disintegration of the myelin sheath and produces fragmentation of the conducting elements of the nerve fibers Kilvington (190)[16] working experimentally with the highly potent tiger snake venom found the most conspicuous necrosis in the cells surrounding the central canal of the cord There was evidence of chromatolysis with degeneration and loss of the Nissl granules disintegration of the nuclear membrane and then complete disappearance of nuclear substance In experimental sheep Fairley[13] describes the effects of a lethal dose of neurotoxin as follows progressive bulbar paralysis is a characteristic finding in sheep the pendulous lower lip dribbling saliva the protruding flaccid tongue combined with an inability to swallow constituting a remarkable and constant picture of the terminal stage Some workers refer to this as a curare syndrome In the earlier stages there is respiratory distress with marked dyspnea due in part to attack on the spinal accessory nucleus in the medulla, with paralysis of the sternomastoid and trapezius muscles, contraction of the

pectorals and compression of the thoracic box all combining to embarrass ventilation Due to palatal paralysis vomitus may be discharged through the nares while loss of the sensory reflex from the larynx may permit its aspiration into the bronchi and bronchioles *Death usually results from respiratory failure*

Snake venom frequently causes hemolysis of the red blood cells in the presence of complement or lecithin in the serum Different elapine venoms vary greatly in their hemolytic capacities Dogs are particularly susceptible and may lose 50 per cent of their corpuscles by lyking within 48 hours after subminimal lethal doses of venom are administered *Hemoglobinuria is a frequent accompaniment* with black masses of hemoglobin crystals in the glomerular capillaries and renal tubules At autopsy there may be a pinkish red staining of the lining of the heart and great vessels and dark reddish pigment in the terminal loops of the mesenteric vessels (Martin 1895)[17]

Viperine and some elapine venoms contain thrombase so that when small amounts are introduced intravenously or larger amounts subcutaneously intravascular thrombosis may occur particularly in the pulmonary and portal vessels with death brought on from circulatory stasis However if the crisis passes without clotting the blood loses its coagulability and additional amounts of venom fail to produce hemocoagulation In some elapine snakes especially cobras *there* is an anticoagulin fraction in the venom which prolongs clotting time Calmette[3] attributed this anticoagulant action at first to destruction of fibrin ferment and later to proteolysis of the fibrin while Houssay and Negrette[18] support the view that it is destruction of thrombokinase

In most viperine snakes including large numbers of American and Old World species hemorrhagins and cytolysins are the most potent and most dangerous fractions in the venom These substances dissolve the endothelial lining cells of the blood and lymph vessels particularly the delicate capillaries There is not only a characteristic breaking down of these vessels in the vicinity of the strike but *in the viscera as well This frequently results in hepatization of the lobules* of the lungs while radial hemorrhage in the cortex of the kidneys is not unusual Likewise the intestinal capillaries mesentery endo- and pericardium adrenals thyroid thymus pancreas and subcapsular zone of the liver are demonstrably damaged (Fairley 1929)[12]

The *local lesion at the site of penetration of the fangs* is characteristically conspicuous in viperine venenation with an edematous red currant like infiltration of the subcutaneous tissues Moreover in this group *endotheliolysis frequently* proceeds centrally along the lymphatic tracts as the venom is carried towards the heart so that both lymphatic vessels and lymph nodes en route partake of the damage In non viperine species hemorrhage is relatively uncommon although local edema is fairly characteristic in fact it may be sufficiently intense after *several hours to conceal the fang punctures*

Usually the fangs enter the skin without puncturing a blood vessel Occasionally the larger snakes with long powerful fangs introduce venom directly into a vein Under such circumstances the venom is carried almost instantaneously to the viscera with rapidly fatal outcome

SYMPTOMATOLOGY

In the elapine group cobras, kraits, etc and in sea snakes there is an intense burning sensation at the site where the venom is discharged into the skin with edema and congestion Soon thereafter there is prostration and sleepiness, incontinence with respect to micturition and defecation salivation nausea, vomiting and cold perspiration There is rapid muscular paralysis with difficulty in speech and swallowing Due to hemolysis the pulse is accelerated and thready The respiration is at first rapid with manifestations of dyspnea and anoxia, then becomes slow and weak, with little or no evidence of thoracic movement, and marked cyanosis supervenes Ocular phenomena include ptosis diplopia and in the late stage dilatation of the pupils, which become insensitive to light Terminal features may include coma and convulsions resulting from asphyxiation Death may occur in a few hours from respiratory paralysis, or if the amount of the venom is sublethal the symptoms may abate rapidly and the patient recover

In viperine poisoning there is an immediate sharp, intense burning pain at the site of the strike with localized swelling and characteristically a bluish or purplish discoloration of the wound Bleeding may be intense or may be absent In a few minutes the pain tends to radiate and becomes excruciating The patient begins to feel nauseated and weak and there is usually a tingling and numbness of the extremities Cold perspiration develops and a feeling of suffocation is experienced Within an hour there may be generalized urticaria with intense itching and burning Meanwhile hemorrhages occur throughout the mucous membranes as well as in the skin they are particularly evident in the conjunctivae and lips and may occasion considerable bleeding There is a parched throat intense thirst extreme prostration, a weak rapid pulse and dyspnea With relatively few exceptions there is no central nervous system involvement If the toxins are lethal in amount death results from repeated circulatory collapse With smaller amounts of venom the symptoms may become less pronounced, and the patient will recover

Not infrequently an ugly necrotic lesion of considerable size develops at the site of the viper's strike due not only to the extensive ecchymosis but to digestive ferments and pyogenic bacteria present in the venom At times tetanus spores from the dirty mouth of the snake are introduced into the wound with possible death from tetanus following convalescence

Diagnosis

The victim usually knows that he has been struck by a snake but if some time elapses before assistance arrives his speech may *have become incoherent* or he may be in a state of advanced respiratory collapse (elapine poisoning) or extreme prostration (viperine poisoning) Marked edema and burning pain at the site of the wound suggest some type of venenation A pair of punctures will indicate that it is not *scorpion or bee sting* *In* snake poisoning these punctures are larger and farther apart than those produced by the black widow spider or centipede but they require differentiation from tarantula venenation In viperine poisoning the marked local reaction with extensive swelling and ecchymosis is relatively *pathognomonic In elapine poisoning the evidence is less distinctive* and even the fang marks may be masked by local edema The train of neurotoxic manifestations is definitely helpful in making a diagnosis in cobra or krait poisoning A knowledge of the geographical distribution of the more common poisonous *snakes should be of assistance in limiting the diagnosis and in instituting treatment*

Prognosis

All front fanged snakes and even the back fanged boomslang cause serious poisoning and all too frequently the death of their victims The outcome of snake poisoning depends on *many factors* most significant of which are the type and amount of the venom the depth of the strike and whether or not the venom is directly introduced into a blood vessel Moreover the physical and mental condition of the patient is important A calm state of mind is of great value in the *outcome while excitement and fear are prejudicial Occasionally individuals* who have suddenly encountered non poisonous snakes have died of fright

Management

This consists in local treatment supportive measures and the administration of antivenin *Local treatment* as Fairley[13] so aptly remarks is for the purpose of *removing* destroying or rendering inert the venom inoculated *into* the tissues before a lethal dose has been absorbed into the systemic circulation It is usually more effective in viperine than in elapine poisoning In some instances of elapine venenation less than two minutes are available after the strike to effect local treatment before absorption takes place *First of all a tight ligature or tourniquet* should be applied around the member above the wound This is most effective around a single bone i e thigh rather than lower leg upper arm rather than forearm At 10- or 15 minute intervals the ligature must be loosened for about

one minute to prevent gangrene In venoms containing considerable thrombase ligation is possibly the most effective single therapeutic procedure but in venoms lacking thrombase ligation merely postpones absorption so that an opportunity is provided for other measures to be carried out

The most important local measure following legation or the one to be accomplished early if ligature is impractical is incision This is at the site of the strike should be cruciform at least a half inch in length and a quarter inch deep to insure free discharge of blood and serum containing the venom It is highly desirable to assist this flow mechanically by a breast type of pump if this is available otherwise by applying the lips to the incision and sucking out the serum This latter procedure usually is not dangerous since the venom is inactivated by digestive juices If there is evidence that absorption is advancing centripetally along lymphatic tracts proximal to the site of incision repeated incisions and aspiration should be performed above the original one In all events unless excessive blood flow has occurred no attempt should be made to staunch the wound with caustics styptics or potassium permanganate, which increases sloughing although mild antiseptics or Epsom salt solution may be used to bathe the wound and if available ice packs to reduce inflammation or edema An intelligent adult or an older child with adequate presence of mind frequently will be able to carry out the simpler procedures on himself when assistance is not immediately at hand

Supportive treatment includes absolute quiet on the part of the victim He should never run about or get overheated Preferably he should be placed in a recumbent position flat on the ground or if possible on a bed and should be covered with a warm blanket but crowding or stuffy air should be avoided Under no circumstances should he take alcoholic stimulants which by aiding the circulation accelerate distribution of the venom through the body Morphine may be given for sedation and barbiturates to lessen pain and nervous tension Strychnine or caffeine will be helpful to prevent collapse In severe poisoning with the development of shock great relief will be experienced and life may be saved by infusion of 500 c c or more of physiological salt solution or preferably blood plasma

Administration of antivenin is intended to neutralize the venom In order to be effective it must contain specific antibodies for the venom of the particular snake or group of snakes It is produced by immunization of horses against the venom of the species of snake which has struck the victim Thus elapine antivenin is not useful in treating patients who have been poisoned by nearctic rattlesnakes or other vipers In practically every country of the world there is at least one central laboratory which produces antivenins for the poisonous snakes of the region The antivenin may be monovalent bivalent or polyvalent The Institut Pasteur de Paris manufactures a polyvalent type against true vipers and cobras

the Burroughs Wellcome Laboratories of London provides a variety of products against snakes in the British possessions the Central Research Institute at Kasauli India manufactures a bivalent antivenin against cobra and daboia venom the Australian Commonwealth Serum Laboratories at Melbourne provides two monovalent antivenins one against the local tiger snake and one against the death adder the Instituto Butantan at Sao Paulo Brazil produces a monovalent antiserum each against the neotropical rattlesnake the Brazilian pit viper or jararaca and the bushmaster as well as polyvalent antisera against rattlesnakes and other pit vipers The Antivenin Institute of America (Mulford s Division of Sharp and Dohme) at Glenolden Pa manufactures three types of antivenin (a) nearctic crotalic for the North American rattlesnakes the water moccasin and the copperhead (b) bothropic for Central American pit vipers and (c) neotropic crotalic for the Mexican and Central American rattlesnake The United States *armed forces in the Western Pacific found nearctic crotalic very effective* in combatting poisoning from the deadly habu *Trimeresurus flavo iridis* of the Riu Kiu Islands while bothropic was inferior No antivenin is commercially *available for coral snake venenation*

Although it is important to utilize snake antivenin at the earliest possible moment this is not as necessary in North American viperine poisoning as in that produced by cobras kraits daboias or the neotropical rattlesnake If nearctic crotalic antivenin is made available within 12 to 24 hours it should be employed *It is put up in 10 c c syringes with a needle sterile and ready for injection* If a physician is available he should administer the antiserum otherwise a layman or the victim himself may inject it Within the first hour or two after venenation it is useful to introduce 2 to 3 c c subcutaneously around the wound to reduce tissue necrosis After two hours the injections preferably should be made more proximally as under the skin of the thigh upper arm or between the shoulder blades The site of injection is first cleansed with alcohol or tincture of iodine then the glass protecting cap is removed from the needle air expelled from the *syringe in the usual manner and the full amount of antivenin introduced* In more advanced cases intramuscular injection is advised in order to obtain more rapid absorption while in collapsed individuals intravenous administration may be justified It is well to be provided with several doses of antivenin for administration at two- to three hour intervals if the patient s condition has not improved *in the meantime Patients are lost because of too conservative treatment rather* than with overdosage of antivenin A final word concerns dosage for infants and young children who have been poisoned they require a larger total dose than adults since a mathematical relation exists between the weight of the body and the amount of venom which it can normally neutralize and dispose of without *injury although the amount injected by the snake is approximately the same* (Hutchinson 1929)[14] In every case it is essential that rational treatment rather

than "home cures" be undertaken The patient should be kept under close observation for at least 24 hours, even though his condition shows marked improvement

PREVENTION

Whenever walking through snake infested country it is practical to wear high top leather boots, preferably coming nearly to the knees If the American Army combat boot is worn, khaki pants should be securely tucked into the top, but there should be free space between leg and cloth both for comfort and as a protection against a snake striking just below the knees Rarely does a terrestrial snake inflict a wound above the knees Unless protected by gauntlet leather gloves the hands should not reach down into brush, undergrowth or under rocks or logs Cotton gloves are probably more of a hazard than bare hands, since they can be rather easily engaged by the fangs of a small snake such as a coral snake or pigmy rattler If a snake is "flushed", it is wise to stand dead still in one's tracks rather than threaten or irritate the snake Frequently it will slink away without causing damage Catching venomous snakes with the bare hands should be left to experienced persons Even they are sometimes caught off guard and occasionally have paid with their lives

Since children are too frequently the victims of venenation they should be particularly watched and cautioned about the dangers of coming in contact with rattlers copperheads moccasins and coral snakes

When camping out of-doors it is important to plan not to sleep on the ground near piles of rocks or brush where snakes may be lurking If shoes or boots are removed at night they should be examined carefully next morning before they are put on since small snakes and scorpions may be hiding inside In walking through jungle growth in tropical America it is well to be on guard against arboreal pit vipers which may strike from above A broad brimmed felt or straw hat is helpful to protect the head and face

As a precaution against accidental venenation it is expedient to carry a first aid kit and a good boy scout knife If a trip is to be made into snake infested country some distance from a physician it is desirable to take along several units of antivenin specific for the type of snake which may be encountered Moreover if a physician is new to an area it would be good judgment for him to inquire about the frequency of snake venenation in the locality and the available stock of antivenin

GILA MONSTERS AND THEIR POISONING

As indicated above under Etiology lizards belonging to the genus *Heloderma* produce relatively severe poisoning of man and lower animals There are

two species both of which occur in the Western Hemisphere *Heloderma suspectum* the true gila monster has a range throughout the semi-desert regions west and south of the Rocky Mountains including western New Mexico southern Utah southern Nevada Arizona the southern part of California and lower elevations in Sonora State Mexico The beaded monster *H horridum* is found from central Mexico through Guatemala and Honduras Adults vary in size 16 to 24 inches for *H suspectum* 36 to 54 inches for *H horridum* They have a typical saurian aspect with a head resembling a truncated triangle with a flattened top a short thick neck a considerably larger longer trunk and a thick tail which is shorter than the trunk and tapers to a conical tip The four short legs are provided with five long finger like toes each with a terminal claw The animal moves along close to the ground usually in a very lazy manner but at times it scampers away from danger moving noticeably from side to-side in its efforts The under side of trunk and tail is covered with scales but elsewhere the body is decorated with a beautiful pattern of small tuberosities resembling Indian bead work Black or purplish black alternates with yellow orange or salmon pink in *H suspectum* black or brownish black with splotches of bright yellow in *H horridum* The natural food of these animals is unknown but probably consists of the eggs of snakes and desert birds possibly at times of small rodents or harmless lizards

In the gila monsters the venom is produced in two enlarged submaxillary glands which bulge out from each side of the lower jaw Arrington (1930)[19] states that from each gland four small ducts lead through four holes in the wide mandibular bone and terminate at the bases of four grooved teeth or fangs These fangs are located in the lower mandible a set of four on each side of the mouth and are small widely separated and curve backward to a slight degree They protrude above the gums little more than an eighth of an inch and each possesses an indistinct groove for conveying the venom secretions A similar number of matching ungrooved teeth are loosely set in the apposed maxilla Some teeth are lost each time the monster bites but are soon replaced from nearby tooth buds

When a gila monster apprehends danger it remains impassive but with its beady eyes at alert attention It may attempt to run away but if overtaken at close range it will emit a hiss open its jaws at a wide angle and pivoting its body on its hind legs strike again and again at the dangerous object Once it has made contact it will snap its jaws shut and maintain a grip like a turtle or a conger eel The small sharp teeth pierce the skin and venom flows through the fang grooves into the wound In many respects the venom has characteristics of snake venom it is a toxalbumin and both physically and chemically has essentially the same reactions (Loeb 1913[20])

The wound produced by the gila monster frequently is severe and lacerating There is considerable swelling and bluish black discoloration of the site The

local pain is sharp, intense and radiating The bite almost invariably occurs on an extremity The entire member frequently is affected, with a tingling sensation accompanied by numbness, but there is no recorded case of this condition extending to the opposite extremity or to the trunk It is not unusual for the patient to experience profuse perspiration, vertigo and a state bordering on narcosis At times tremors may be observed, which have been attributed to severe intoxication However, there is no evidence of respiratory failure or circulatory collapse Thus the train of symptoms suggests that the venom contains a neurotoxin which temporarily affects the motor centers while hemotoxins appear to be lacking or, if present, to constitute a very small fraction of the total venom There is no authentic record of death due to gila monster poisoning per se (Storer 1931 [1])

First aid measures of ligature, incision and cupping are useful in gila monster as in snake venenation Symptomatic treatment should be used to reduce pain and caffeine may be administered to prevent narcosis Thus far no specific antivenin has been developed Even greater precautions should be taken than in snake poisoning to counteract bacterial infection introduced into the wound from the foul mouth of the monster Probably topical application of sulfonamides will be sufficient, if early attention is given to this possible complication

Summary

Poisonous snakes are widely distributed over the face of the globe Although the incidence of snake bite is comparatively low the mortality of untreated or inadequately treated cases is very high All snakes secrete poison which is elaborated in modified parotid glands Only those which have special canalized teeth called fangs are dangerous to man The fangs consist of a functional pair, one of which is set in each maxilla Back fanged snakes, *Opisthoglypha*, are relatively harmless to man because of their difficulty in introducing the fangs into the skin The boomslang of East Africa constitutes a notable exception Front fanged snakes are of two types (1) the elapine forms (cobras kraits mambas coral snakes Australian poisonous snakes) and sea snakes all of which inject venom consisting primarily of neurotoxic elements and (2) the viperine forms (true vipers rattlers copperheads moccasins bushmaster, fer de lance and other pit vipers) whose venom contains large amounts of hemolysin and cytolysins In the Western Hemisphere there are only the group of the pit vipers and the coral snakes in Europe only the true vipers in Australia only elapine species in Africa and Asia both elapine and viperine snakes

The venenating capacity of a particular snake depends on the size of the snake and the corresponding amount of venom elaborated and secreted on the potency of the venom and its particular type of toxins and on the efficiency of

the striking mechanism of the snake Furthermore some snakes are relatively phlegmatic and will not strike a human being unless antagonized while others are very belligerent and will attack without apparent provocation A few elapine species spit venom to a distance of several feet and produce temporary or permanent blindness Poisonous snakes may be encountered at times in the home or garden but more frequently they occur in timbered or jungle areas in rocky canyons or on sandy wastes Most snakes can not strike above knee height The members of the body most frequently attacked are the foot ankle lower leg fingers hand wrist and forearm because these parts of the body are most likely to come in contact with the head of the snake The victim may be struck at work or at play rarely when asleep

Snake bite almost invariably produces a burning pain with edema at the site of injury In elapine and sea snake poisoning the neurotoxic venom is absorbed rapidly and within a few hours produces a severe frequently fatal motor paralysis with terminal respiratory failure In viperine poisoning there is a more serious local wound with purplish swelling resulting from lysis of the walls of the blood vessels Although the toxin is disseminated somewhat more slowly than neurotoxin it causes fairly rapid hemolysis and hemorrhage throughout the mucous membranes skin and viscera leading to circulatory collapse If either type of venom is injected directly into a vein the systemic distribution is very rapid Diagnosis of snake poisoning usually is not difficult to make on the basis of a bite in snake infested regions the appearance of the local injury and the train of symptoms A knowledge of the types of snakes present or prevalent in a geographical region will aid in determining the particular management best suited for the patient

First aid measures consist in application of a tourniquet cruciform incision at the site of the strike and suction to extract the venom before it becomes distributed throughout the system The victim should lie down and abstain from alcoholic stimulants Morphine may be used to alleviate the pain and barbiturates to reduce nervous tension Strychnine or caffeine may be used to combat collapse but infusion of physiological salt solution or plasma is most likely to produce satisfactory results Specific monovalent or polyvalent antivenin is available in practically every country against the more important venomous snakes of the region and should be administered wherever possible In the neurotoxic type of poisoning it must be employed very soon after venenation in order to be beneficial in the hemolytic and hemorrhagic type it may be administered even up to 24 hours after the venom has been injected and still be useful Larger amounts are required for children whose system is not able to neutralize as much of the toxin as that of a grown person

Precautions against snake poisoning consist in wearing good leather boots when tramping through undergrowth wearing gauntlet leather gloves before

reaching into piles of brush or stones, not sleeping on the ground near snake lairs not picking up snakes bare handed, protection for the head when traveling through areas where arboreal snakes abound Special attention should be directed to children who are most likely to encounter snakes while at play A first aid kit, good pocket knife and an adequate amount of specific antivenin should be in the equipment of hunters, trappers fishermen, explorers or persons walking through regions which are infested with venomous snakes

Two species of lizards *Heloderma suspectum* of the southwestern United States and *H horridum* of Mexico and northern Central America, elaborate venoms and at times produce poisoning in man These saurians have four fangs arising from each mandible with apposing maxillary teeth Each fang is supplied with venom elaborated in a submaxillary gland On contact with the extremity of a person the jaws of the lizard snap shut, and a multiple lacerating wound is made There is a painful, inflamed lesion at the site and tingling with numbness of the entire member General symptoms are relatively mild with profuse perspiration vertigo and toxic narcosis No deaths have been recorded as a result of *Heloderma* poisoning First aid and supportive treatment are similar to those carried out in snake poisoning There is no antivenin available

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CHAPTER XX

THE TYPHOIDS

(TYPHOID AND PARATYPHOIDS A, B AND C)

By HOBART A. REIMANN

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Synonyms — English enteric fever German Typhus Abdominalis

It has been the custom to describe typhoid and the paratyphoids in separate places Yet they are clinically indistinguishable, and the group of bacilli which cause them are so closely related that the diseases may be regarded as a group of similar entities and described together The present manner of classification of the causative bacilli as *Eberthella typhosa, Salmonella paratyphi Salmonella schottmulleri* and *Salmonella paratyphi C* is clumsy and confusing Classification could be simplified by replacing these hybrid words with numerals or letters as in the case of *Pneumococcus* or *Streptococcus pyogenes* The differences between typhoid bacilli and the paratyphoid bacilli are no greater than those for example, between pneumococci of type 1 and pneumococci of type 3 Aside from offending tradition there seems to be no valid objection to naming the cause of typhoid as *Bacterium typhosus* group 1, type A B or C etc those of paratyphoids as *Bacterium typhosus* group 2, group 3 and so on and naming the respective diseases accordingly

History

Because various acute enteric infections may resemble each other clinically and often may be confused with other diseases as well little progress was made in their classification until early in the nineteenth century Many descriptions of disease which may have been typhoid appear in ancient medical writings, and one of the first fairly clear pictures of the disease is credited to Spigelius in 1624 Thomas Willis in 1684 described a disease called putrid fever" or ' flux of the belly ', which most likely was typhoid noted "pustules" in the intestine and differentiated it from *febris pestilens* probably typhus Confusion, however, persisted In 1804 Prost also demonstrated the association of intestinal lesions with the disease as did the French clinicians Bretonneau, Petit and Serre in 1813 Chomel mentioned perforation during the disease An American, Nathan Smith left an accurate description of typhoid in 1824 and was perhaps the first to point out its infectious nature[4]

The French clinician Pierre Louis in 1829 gave a full account of the disease and named it typhoid fever to indicate that it is like typhus or smoke because of the clouded sensorium so often present Despite the evidence at hand typhoid still was confused with typhus and with other diseases until 1836, when W W Gerhard of Philadelphia, a pupil of Louis, in a classic of medicine established

anatomical and clinical proof of the differences between typhoid and typhus Even after this advance in thought many remained unconvinced until general opinion finally was influenced in the right direction by the efforts of Elisha Bartlett in 1842 William James in 1850 George Shattuck James Jackson Alfred Stille and others So far as its infectiousness was concerned Murchison as late as 1873 still believed typhoid to originate from decomposing material He was refuted by a pioneer epidemiologist William Budd in a study published in the same year Budd was the first to trace infection to water contaminated by excreta from typhoid patients this was done in 1850 These observations were remarkably astute since they antedated the discovery of bacteria by many years

Apparently little attention was given to the new concept of the infectious nature of typhoid from a practical point of view and no special attempts were made to control typhoid which was one of the chief causes of death in the Civil War of 1861–65 the Franco-Prussian War of 1870 the Spanish American War of 1898 and even as late as the Boer War of 1899–1902

The causative agent *Eberthella typhosa* was described as seen in tissues at necropsy in April 1880 by Klebs in July of 1880 by Eberth and in 1881 by Koch but as its present name indicates credit is given to Eberth The bacillus was cultivated in 1884 by Klebs and by Gaffky and was isolated from feces by Pfeiffer in 1885 from the urine by Hueppe in 1886 from the blood by Fraenkel and Simmonds in 1886 and Vilchur in 1887 and from the gallbladder by Gilbert and Girode in 1890 The discovery of the typhoid bacillus as the cause of the disease ended controversy as to the specificity and infectiousness of typhoid An important discovery to aid in the diagnosis of typhoid was the demonstration of a specific agglutinin for the bacillus in the blood of infected animals by Gruber and Durham and in human patients by Grünbaum and Widal in 1896 now applied as the Gruber Widal test or the Widal test The development of special culture media led Conradi and Drigalski to discover healthy carriers by cultivating *E typhosa* from the feces in 1904 In 1907 Soper s investigation of Typhoid Mary brought the matter of the healthy carrier forcibly to attention

It became evident that bacilli not specifically *E typhosa* caused disease indistinguishable from typhoid which led to the discovery of a variety of so-called paratyphoid bacilli by Achard and Bensaude 1896 Gwyn 1899 and Schottmüller 1900 the chief of which are *B paratyphosus A* now called *Salmonella paratyphi B paratyphosus B* now called *Salmonella schottmulleri* and *B paratyphosus C* now called *Salmonella paratyphi C*

In 1896 Pfeiffer and Kolle and Wright and Semple introduced prophylactic vaccination with heat killed typhoid bacilli a procedure which together with improved sanitation based on a knowledge of the epidemiology led to the great decline in the incidence of typhoid wherever these measures are applied Further impetus to the diminution of typhoid in the United States came from the efforts

Synonyms — English, enteric fever German Typhus Abdominalis

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acid but no gas is produced which aids in their differentiation from the salmonellas When grown in bismuth sulfite media the colonies have a metallic black sheen colon bacillus colonies usually are white and those of the salmonellas greenish The cell substance is toxic for experimental animals but no soluble toxins are formed

Bacilli are killed by temperature at 55° C to 60° C for 30 minutes and by the usual chemical bactericidal agents Various strains resist streptomycin in



FIG 1 Electron micrograph of *E typhosa* The bacilli had been exposed to rabbit antityphoid serum The bacilli and flagellas are therefore thickened from a coating of antibody globulin The clear spaces are caused by shrinkage of the inner protoplasm and its separation from the protoplasmic membrane (Mudd S and Anderson T F Jour Am Med Assoc 1944 CXXVI 570)

concentrations of 6 to 30 micrograms per c c of broth They are not influenced by the usual concentrations of sulfonamide compounds or by penicillin Bacilli do not propagate naturally outside the human body so far as is known They are killed easily by sunshine and drying but survive in ground water for 2 or 3 weeks and in fecal matter protected from the weather for 1 to 5 months They may be carried for many miles in rivers and survive longer in pure water than in

of the American Medical Association which made and published annual surveys of typhoid in the cities of the United States beginning in 1913

Surprisingly little progress has been made in the treatment of typhoid as shown by an unchanging mortality rate Aside from the gradual abandonment 30 or 40 years ago of the barbarous ice bath treatment the chief contribution has been the replacement of the starvation treatment with a liberal diet by Coleman who had great difficulty at first in popularizing his views and was even threatened with legal action So far the only agent, which has a specific action against *E typhosa* in culture media is streptomycin discovered by Waksman in 1942

Etiology

The typhoid bacillus is known by several names, *Bacillus typhosus Bacillus typhi Bacterium typhosum* but it is officially recognized now as *Eberthella typhosa* It is related closely to other bacilli of the enteric group or family *Enterobacteriaceae* and with them is included in the species *Eberthella* as one of three genera of the tribe *Salmonellae* The other two genera are the *Salmonellae* including the so called paratyphoid bacilli and shigella or dysentery bacilli

This classification is not acceptable to all bacteriologists but serves as a working basis at present It would seem more desirable to adopt classification by letters or by numbers similar to that applied to hemolytic streptococci for example the typhoid bacillus as group 1 subtypes A, B, C, etc , the paratyphoid bacillus A as typhoid bacillus, group 2 with subtypes and so on as suggested in the introduction Progress in knowledge of the typhoid group of bacilli up to 1939 is summarized in a review by Weil Gall and Wieder[40]

Morphology and Staining — The typhoid bacillus cannot be distinguished morphologically from other members of the enteric group It is a short rod varying from 1 to 3 5 microns long by 0 5 to 0 8 microns broad From agar cultures short forms predominate and from broth, longer ones Active motility is provided by 12 to 14 flagellas (Fig 1) The body contains what appear to be vacuoles or metachromatic granules but no spores It is readily stained with the usual dyes and is decolorized by Gram s method

Growth — Growth occurs readily on the usual media in a temperature range of 4° C to 45° C best at 37° C and in a pH range of 5 to 8 6 best at pH 6 8 to 7 Colonies on solid media usually are smooth, bluish white, translucent, flat domes The colony edges often are notched irregularly Dissociation into the rough form may be noted in flatter, rough and more opaque colonies Opaque yellow colonies have been described Small colony variants may be associated with the disease[77]

Gelatin is not liquified no indol is formed nitrates are reduced to nitrites hydrogen sulfide is produced Typhoid bacilli are weak fermenters of sugars

Distribution of Bacilli in the Body

Lymphoid Tissue and Blood — Typhoid bacilli probably invade the body chiefly through the lymphoid structures of the small intestine but perhaps also of the oropharynx and esophagus The site of the multiplication of bacilli is uncertain but appears to be in the lymphoid tissue of the intestine and mesentery rather than in the feces or blood According to Goodpasture[1] bacilli in their usual morphological form are present in macrophage cells and smaller variant *forms are present in the cytoplasm of young plasma cells of the lymphoid follicles* in the mesenteric lesions[2] Young plasma cells may be the essential cellular host The Peyer s patch mesenteric lymph node complex therefore seems to constitute a focus of infection analogous to the lesion lymph node complex of tuberculosis From this complex bacilli invade the blood stream and are disseminated throughout the body It is possible that at times bacteremia occurs first and bacteria reach the intestinal tract by way of the blood

Bacilli are perhaps always present and usually are demonstrable in the blood in the first week of the disease Since they probably do not multiply here the condition is a bacteremia rather than a septicemia Bacilli are present progressively less often in the blood as the disease advances As a result of the distribution by the blood bacilli reach most of the organs and tissues of the body where they may or may not establish themselves Their predilection for lymphoid tissue and cells explains their presence in lymphoid tissue in the spleen liver lymph nodes bone marrow gall bladder rose spots and elsewhere in the body

Intestinal and Biliary Tracts — Here as elsewhere bacilli select the lymphoid structure They are retained in the tissues until necrosis and ulceration permits their escape into the bile or feces This accounts for their relative infrequency in the feces until after the first week when shedding occurs They enter the feces from two sources from the intestinal lesions and from the biliary tract during the disease and at times afterward Bacilli may be present in the feces of carriers before the onset of disease As a rule they are present in feces in diminishing numbers from the duodenum to the rectum suggesting that the main source is high in the intestine or in biliary tract and that feces is not a favorable matrix for their existence In certain instances of undoubted typhoid bacilli are retained in the tissues and cannot be cultivated from any of the usual sites They are most constantly present in the feces during the second week (Fig 2) and disappear by the fourth week except in prolonged disease and in carriers Bacilli are seldom present in the stomach and vomitus unless the duodenal contents are regurgitated but like colon bacilli they may be cultured at times from the oropharynx

Since bacilli of the typhoid group grow in bile-containing media they find *circumstances favorable for growth in the lymphoid tissue and contents of the*

water contaminated by sewage Typhoid bacilli, when injected into laboratory animals may give rise to a disease but unlike that seen in man

Antigenic Structure — Great advances have been made in recent years in the knowledge of the antigenic structure of typhoid bacilli which need not be detailed here[40] Most strains especially those isolated from patients in addition to the somatic or "O" antigen and the flagellar or "H" antigen associated with the S–R phase transformation, have a Vi antigen[10], which was thought to be associated with the virulence, and which disappears on continued transfer on media The significance of these dissociative and other changes to the epidemiology of typhoid and to the disease itself is not clear The formula of the antigenic structure of *E typhosa* is IX, XII d —

Bacteriophage Typing — Craigie and Yen[17] showed that Vi containing typhoid bacilli can be classified according to the lytic effects of classified bacteriophages The types and subtypes were found to be stable and were named A, B_1 B_2, C and so on to the letter J Typing is a simple procedure made by inoculating a series of places on an agar surface with bacilli then superimposing an inoculum of the respective types of bacteriophage on each area After incubation the area in which lysis occurs, represents the type of typhoid bacillus present[1] Typing of the bacilli is of value in epidemiology to aid in tracing the source of infection and otherwise[36] In one study[27] 72 per cent of 1,485 cultures was composed of types A, E and C

Paratyphoid Bacilli[5] — Bacilli of this large group resemble *E typhosa* morphologically and tinctorically but differ in antigenic nature and in ability to ferment various sugars upon which bacteriological differentiation depends They are distributed widely in man, in animals and in birds In man paratyphoid bacilli give rise to widely different forms of disease, one almost identical with typhoid another a sudden, stormy, short lived infection usually called food poisoning and others with septicemia and localization in various organs There is no explanation for these striking differences in the clinical reaction of man to infection

The three varieties of paratyphoid bacilli most often associated with disease in man are (1) *Salmonella paratyphi* (*B paratyphosus A*) This form differs from others by its inability to ferment xylose, and it is serologically distinct It is found in human carriers and in sewage (2) *Salmonella schottmulleri* (*B paratyphosus B*) is easily distinguished from *S paratyphi* but not from others of the group The source of infection with this usually is of human origin, but also it exists in dogs and cattle (3) *Salmonella paratyphi C* is encountered chiefly in Asia, Africa and southeastern Europe It is closely related to *Salmonella suipestifer* or "hog cholera" bacilli and little is known of its epidemiology For further discussion of the salmonella organisms *see* Oxford Medicine, Vol IV Chapt XXI

Paratyphoid bacilli especially *Salmonella paratyphi C* may cause septicemia primarily they may not cause intestinal lesions and therefore may not appear in the stool They are found in the pus of pyarthrosis and in the lungs when pneumonia occurs

Epidemiology

Since *E typhosa* is never found in animal hosts and does not multiply or live long outside the human body man so far as is known is the only reservoir and source of infection This being the case together with the fact that infection enters only through the mouth the control of typhoid would seem to be a comparatively simple matter If it were possible to eliminate the carrier state or to destroy all bacilli as they leave the body or afterward or to prevent their ingestion or to immunize all people solidly against infection typhoid like cholera and other enteric infections could be exterminated Unfortunately the epidemiology of typhoid is complex and often obscure It concerns the sources of infection in patients and especially in carriers which for the most part are undetectable or uncontrollable the multitude of variable incidents and circumstances which transpire between the time bacilli leave the sources and enter the mouths of new hosts and the variable state of resistance by natural or acquired immunity or the susceptibility of the new hosts By attacking the problem at each of these points much indeed already has been done to reduce the incidence of epidemic typhoid in places where the proper procedures are carried out In fact the only progress in the control of typhoid has been along these lines no progress has been made in specific treatment until recently

From an epidemiological point of view typhoid may be discussed as epidemic and as endemic sporadic or residual Both forms arise from patients or carriers whose bacillus bearing excrement reaches beverages food fomites and other articles

Epidemic Typhoid — Large outbreaks of typhoid seldom occur in places where hygienic measures are in force as just stated yet accidents or errors in technic may occur at any time even under ideal circumstances to cause them In many parts of the world where few or no measures are observed large outbreaks still occur

Contaminated water is the chief cause of sudden large epidemics milk and other foods of lesser ones Raw water of reservoirs lakes or rivers used to supply large communities is contaminated chiefly by untreated sewage or by alvine discharges deposited in or near it Bacilli live for days or weeks in water depending upon its mineral or organic content its temperature rate of flow and degree of pollution and may be carried for miles in streams Water from wells which causes localized small outbreaks is contaminated by seepage from poorly located and

gall bladder and biliary tract where they may reside for decades to establish the carrier state From here constantly or intermittently they may enter the feces during the disease or afterward

Presence of Bacilli Elsewhere — Bacilli in the blood obviously reach the kidneys and escape into the urine from which they can be cultivated in about 25 per cent of patients (Fig 2) yet they seldom become established there In unusual in

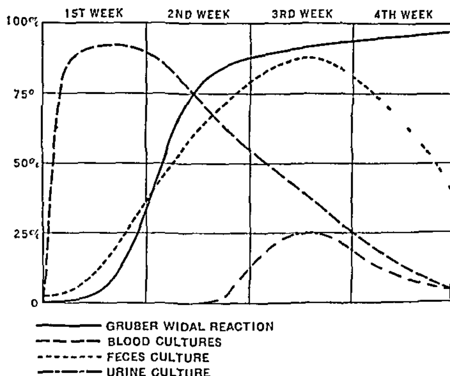


Fig 2 Approximate percentage of positive results with different laboratory diagnostic tests for typhoid according to the week of disease in an attack of average duration (from Park & Williams Pathogenic Microorganisms Lea and Febiger 1939)

stances they may give rise to pyelonephritis pyelitis and cystitis They may be excreted in the urine for months or years Bacilli may be excreted in seminal fluid

In rare instances bacilli of the typhoid group may cause hematogenous pneumonia and appear in the sputum and in the pus of empyema In typhoid meningitis bacilli are present in the meninges and spinal fluid and perhaps in the brain substance as well during encephalitis They may cause mastitis and enter the milk They are said to be excreted at times in sweat Bacilli are present in the various suppurative lesions, particularly in bones, where they may persist and be discharged for years

touch them may easily convey infection to their mouths Nurses and attendants of typhoid patients may have transient typhoid bacillus bacteremia bacilluria and shed bacilli in their feces yet remain well Typhoid may be contracted by *swimming in contaminated water*

Immunity — In a given population great variations of specific or non specific immunity or resistance to typhoid exist As with most other infections good nutrition healthful work mental ease and prosperity are all non specific features conducive to resistance as opposed to famine war pestilence overcrowding and poverty *In every epidemic no matter how severe many exposed persons escape* both actual or inapparent infection As stated in the preceding paragraph some of these may have harmless transient bacteremia It is assumed that some of these resistant persons have either non specific immunity or specific immunity from a previous attack of the disease or from vaccination An attack of typhoid *confers a degree of immunity in most patients for a variable length of time* The same may occur although less solid in vaccinated persons Yet in both subsequent attacks of typhoid may occur About 2 per cent of typhoid patients have had a previous attack In one patient 3 attacks occurred in 6 years A large number of attacks have been reported in persons apparently adequately vaccinated[7 5]

Specific agglutinins for the typhoid paratyphoid group of bacilli and the specific protective power of the serum as demonstrated in mouse protection tests are demonstrable indications of immunity Agglutinins are not always present with protective bodies but they are not present except in serum containing protective substance In other words the demonstration of agglutinin in the serum indicates a degree of immunity but a person may be immune without demonstrable agglutinin in the blood Persons whose blood gives a positive Widal *reaction however may contract typhoid*

Agglutinins begin to appear after the fifth day of disease and are present in 80 to 90 per cent of patients by the fourth week in titers usually of 1 320 to 1 640 occasionally to 1 20 000 or more Agglutinins diminish later and disappear in 60 per cent of persons within 7 months They may persist for years in low titer *of 1 80 particularly in carriers Agglutinins may be reactivated by* specific or non specific vaccination and by other infections especially by typhus and brucellosis as an anemnestic reaction Conversely agglutinins for other bacteria such as the brucellas for example may be stimulated to high titer by typhoid

CARRIERS

Carriers are healthy persons with or without a previous record of typhoid who harbor typhoid bacilli in their body and excrete them continuously or inter

badly constructed privies, by leaking sewer pipes and by fecal matter washed in by surface water Pure water may be contaminated by distribution in soiled containers by adding contaminated ice or otherwise All persons who drink typhoid bacillus bearing water regardless of age sex or economic status are liable to infection Water borne epidemics may occur in any season but particularly in late winter and early spring Ice made from contaminated water may convey infection since typhoid bacilli may survive in it for several months

Milk may be contaminated during milking processing or distribution by the hands of a carrier soiled with his feces or urine by placing milk in containers washed with contaminated water or by diluting it with the same Outbreaks have been traced along a milkman s route in the days when milk was carried in cans and ladled into consumer's containers Inspection and control of dairies, pasteurization and the bottling of milk have greatly reduced this danger, but carelessness and accidents still account for sporadic outbreaks Ice cream may serve as a conveyer but butter and cheese rarely do

Food borne epidemics seldom are extensive An epidemic of at least 60 patients and 8 deaths occurred in the winter of 1945 in Philadelphia among patrons of a bakery where a carrier unwittingly inoculated cream filled pastry with type F bacilli Carriers who handle food are the chief culprits of such outbreaks the most notorious of which was Typhoid Mary a cook, who in the course of her migration from employer to employer caused at least 7 small epidemics, 53 known attacks and 3 deaths until she was kept in an institution[51] Shell fish from contaminated waters especially near large communities cause small outbreaks Lettuce celery water cress and other vegetables eaten raw may carry infection if grown in or washed or sprayed with polluted water Any kind of food or drink may be contaminated by crawling or flying insects which previously have alighted on typhoid bearing feces or urine Insects may carry infection for several weeks They are of especial danger on farms or in camps near open privies Dust rarely conveys infection since typhoid bacilli are not resistant to drying and sunshine

Endemic Sporadic or Residual Typhoid — Even if large epidemics can be prevented by the measures outlined on a subsequent page residual typhoid will occur as long as carriers exist and as long as breaks in technic of those who come in contact with typhoid patients occur According to Cay statistics of 7,000 cases show that from 4 to 32 per cent of patients contracted their infections from carriers Typhoid may arise in carriers themselves from the bacilli they harbor

Sporadic attacks of typhoid may arise as described in the preceding sentence or may occur in persons infected by close association with a typhoid patient or a shedding carrier whose clothing bedding towels bath water eating utensils bedpans urinal catheter enema tube clinical thermometer or any other personal articles may be soiled with excrement Bacilli may survive for days on most of the items mentioned and unless proper measures are taken, persons who

PREVALENCE OF THE TYPHOIDS

Typhoid occurs in all parts of the world and reaches large epidemic and endemic proportions in places where hygiene and sanitation are not in force The paratyphoids occur less frequently in the United States than elsewhere Statistically they are usually included with typhoid itself Increases of incidence occur especially *in time of war pestilence famine and other catastrophes* In countries and communities where sanitary practices are in force the incidence of typhoids has been greatly reduced especially in cities After 19 0 it was seldom necessary to set aside special typhoid wards during the summer months

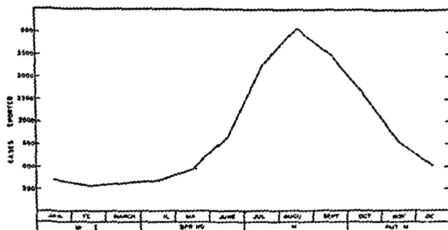


FIG 3 The seasonal incidence of typhoid and paratyphoid Averages of reported case by months for the years 1930 to 1938 (Data from Supplements to U S Public Health Reports from Jordan and Burrows Textbook of General Bacteriology W B Saunders and Co 1945)

in urban hospitals Certain cities of Europe and in this country report no typhoids at all for long periods but as explained in the section on Epidemiology accidents and carelessness may cause sporadic cases or epidemics at any time Typhoids especially in sporadic or small epidemic form are more common in rural areas and in warm climates They occur throughout the year but more commonly in the late summer and early fall months as shown in Figure 3 The seasonal prevalence in warm months has not been explained satisfactorily but several factors may be mentioned more fluids are drunk vacation travel is greater flies are more abundant and higher temperature may be more favorable to the survival or growth of the bacilli outside the body

Statistics — Official statistics of the incidence of the typhoids are mostly mere approximations Even in 1943[30] in many places where better could be expected typhoids were reported irregularly to city or state health officials or not

mittently Ambulatory patients with mild attacks of typhoid may be regarded also as carriers

As a rule, after an attack of typhoid the causative bacilli rapidly disappear from the stool In about a third of convalescent patients bacilli may persist in the feces for 3 weeks in a smaller number they persist for months, and exceptional patients 3 per cent become permanent carriers Persons who have never had typhoid, may be carriers Persons who are carriers may acquire typhoid from their own bacilli

Evidence suggests that in carriers bacilli establish themselves chiefly in the biliary tract and upper intestine and are shed intermittently or constantly into the feces Bacilli which are excreted in the urine, probably are harbored in the pelvis of the kidney, the urinary bladder or elsewhere in the genitourinary tract From 10 to 25 per cent of patients shed bacilli in their urine during early convalescence

Combined fecal and urinary shedders are rare Bacilli may be discharged for years in exudates from chronic lesions of bones In most cases bacilli are shed intermittently with periods of freedom for weeks or months, this often makes the detection of carriers difficult and easily may mislead investigators to regard them as permanently "cured" after testing various therapeutic measures

According to Ames and Robins women are chronic carriers more often than men in the ratio of 3 8 to 2 1 per cent Adults are carriers more often than children The frequency of carriers in a population varies from 0 to 12 per cent according to the community and depending upon current or past local typhoid infection sanitary conditions and the social and economic level According to estimates the carrier rate in the general population is about 45 per 100 000 Considering the difficulties in detecting carriers the estimate is too low With constantly improving sanitary conditions the actual rate may be expected to decline

Carriers can be identified only by isolating bacilli of the typhoid group from their excreta or discharges by repeated examination because of the intermittent excretion of bacilli Cultures may be obtained with the duodenal tube While the Widal reaction is positive to some degree in most carriers, it may be positive in those who are not carriers as a result of vaccination or from the disease itself More reliable for detection of carriers is the presence of antibody to the Vi antigen which occurs in most carriers but seldom after vaccination[19]

The recognition and control of carriers is one of the key factors in the control of typhoid Carriers who observe all the rules of hygiene and do not handle food or drink for others are of no immediate danger to others Carriers who violate rules may require incarceration in institutions Their treatment is described on a later page

typhoid dropped from 198 to 71 the next 2 years after vaccination was compulsory the incidence fell to 27 and to 4[7] Vaccination was not responsible for the diminution of typhoid noted in the country at large since it was not used generally at this time The sharp peak of increase in 1916–1917 was due to a great increase in the size of the Army greater exposure during camp life and to some extent to the increase of paratyphoid fever against which vaccination

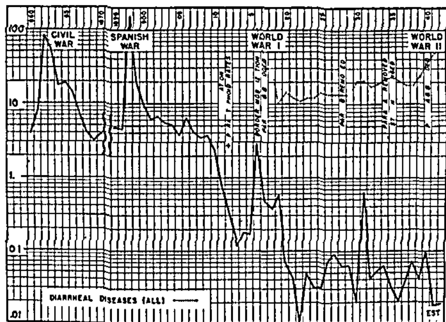


Fig 4 Rates per thousand annually for typhoid in the United States Army 1860–1942 Dotted line shows rates for all diarrheal diseases (from Callender J R and Luippold Jour Am Med Assoc 1943 CXXIII 319)

was not effective until paratyphoid bacilli were added to the vaccine It is noteworthy that during the striking decline of incidence noted no change occurred in the case fatality rate

In many parts of the world typhoid is still a serious menace In the summer of 1945 typhoid was one of the most common infectious diseases in Chungking Calcutta and Cairo during the author s visit

Sex —Except in children where the incidence is the same slightly more than half of the cases of typhoid occur in males This may be explained by greater chance of exposure during out door work greater mobility consumption of more water and less fastidiousness among men than women

at all Health officials themselves at times are reluctant to collect or submit accurate and complete figures because of false civic pride or for other reasons In many places deaths from typhoid alone are reported so that only an approximation of the incidence of the disease can be estimated by calculation from the average mortality rate Statistics from the Armed Forces are the most accurate but reflect the incidence among a selected group of persons However, these are men in the age most affected by typhoid

Typhoids have greatly diminished in the United States in Europe and elsewhere where sanitary measures have been in force during the past 40 years Many factors have contributed to the decline especially the application of accurate knowledge to the control of water milk and food the recognition and control of carriers and patients general education, a rise in the standard of living and perhaps least of all vaccination The accurate etiological diagnosis of diseases which may resemble typhoids clinically and be mistaken for them, such as typhus malaria brucellosis tularemia viral pneumonias, psittacosi ornithosis and others, by exclusion has reduced the statistical incidence

According to samples of the statistics assembled annually by the American Medical Association since 1913 the estimated typhoid rate for 78 cities of the United States has declined as follows

	Population	Typhoid Deaths	Typhoid Death Rate per 100 000
1910	22 5 3 000	4 637	20 54
1915	25 713 000	2 434	9 47
1920	28 244 000	1 088	3 85
1930	34 410 000	554	1 61
1942	35 895 000	83	0 23
1945	35 895 000	80	0 22

The death rate in the Southern states is several times higher than elsewhere By arithmetic one can roughly estimate that in 1910 in the United States as a whole about 30 000 persons died of typhoid and in 1945 about 350 If the mortality rate is 10 per cent, about 300 000 cases probably occurred in 1910 as compared with 3 500 in 1942 Many more cases and deaths occur than are reported

The incidence of the typhoids in the selected personnel of the Army over an 80 year period is illustrated in Fig 4 These statistics emphasize the effect of war on typhoid In the Civil War, Franco-Prussian War, Spanish American War and the Boer War typhoid caused more deaths than battle wounds[4] In the U S Army during World War I there were only 1 529 cases and 227 deaths If the incidence had been the same as in the Civil War there would have been 200 000 cases and 30 000 deaths In World War II up to 1944 the incidence of typhoid paratyphoid was one tenth that of World War I As shown in Fig 4 a great drop in typhoid occurred in 1910 and 1911 when antityphoid vaccine was first used Vaccination was voluntary in 1910 but by 1911 the incidence of

The characteristic typhoid ulcer of a Peyer s patch in the lower part of the ileum is somewhat oval its long axis parallel with the long axis of the bowel The base usually is smooth the edges thin and undermined The most advanced ulcers usually are found in the region of the ileocecal valve gradually showing earlier stages higher in the bowel In severe cases the lower end of the ileum may be converted into one large ulcer involving the whole wall with only islets of mucosa remaining

The histological picture evolves as follows (1) The lymphatic tissue (Peyer s patches) early becomes hyperemic hyperplastic and projects above the level of the surrounding mucosa The borders are sharply defined usually vertical at times overhanging Microscopically at this stage there is evidence of hyperemia



Fig 6 Hyperplasia and swelling of part of a Peyer s patch with superficial ulceration and necrosis in the second week of typhoid

and proliferation of plasma cells and macrophages in lymphoid tissue with peri follicular hyperplasia Typhoid bacilli may be seen in the hyperplastic areas[9] (2) By the beginning of the second week portions of the follicles undergo necrosis from toxic effects from local vascular obstruction or from pressure from hyper plastic tissue (Fig 6) (3) The central portion of the plaques sloughs away first leaving a smooth base The edges of the ulcer however remain swollen and infiltrated Dilated vessels are eroded The base of the ulcer may be the muscular coat or the ulcer may extend through the wall leading to local peritonitis or to perforation It is during this stage of sloughing that hemorrhage or perforation is most apt to occur (4) The process of healing varies depending upon the intensity of the injury Not all involved Peyer s patches undergo necrosis Where the process is less severe the hyperplastic elements are absorbed and the plaques return to normal Where sloughing has occurred the borders beyond the

Age and Race — All ages and races are liable to infection but the prevalence of typhoid is greater in youth and early adult life with its greatest frequency between 10 and 30, highest at 20 Eighty per cent of attacks occur between the ages of 15 and 35 In the civil population 50 per cent of typhoids occur in one sixth of the population Typhoid may occur in the fetus

PATHOLOGY

The pathology of the typhoids includes lesions which are non-specific and due to the febrile condition The characteristic histological lesion of typhoid is composed of a collection of mononuclear cells chiefly macrophages, which make up the granulomatous lesions (Fig 5) or "typhoid nodules' as found in the liver, spleen bone marrow and lymphatic tissue in any organ [6]

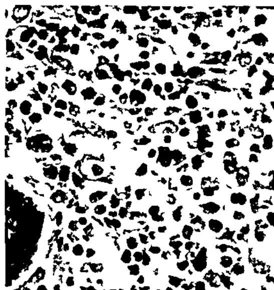


FIG 5 Essential cellular reaction of typhoid in an area from Fig 6 showing macrophages plasma cells lymphocytes and a few reticular cells Typhoid bacilli in clusters may be seen occasionally in the plasma cells and macrophages

Intestine — The gross almost pathognomonic features of typhoid are in the small intestine Here the lesions of the Peyer's patches may be classified according to their evolution as (1) invasion and hyperplasia (2) necrosis (3) ulceration and sloughing and (4) healing The 4 stages overlap but roughly parallel the clinical picture in the respective 4 weeks Lesions in different stages may be present at the same time The process in mild attacks may not pass the first stage

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necrotic areas become hyperemic and hemorrhagic infiltration may occur Gradually the cellular elements in the periphery proliferate and extend over the denuded area until the original continuity of the epithelium is restored When ulceration is extensive restoration may be incomplete so that the floor of the ulcer is covered with connective tissue containing few or no glandular elements Healed ulcers often may be recognized by their smooth pigmented surface often depressed below the surrounding mucosa

Perforation — In the majority of cases perforation occurs within 18 inches of the ileocecal valve The perforation may be in the appendix or the large bowel, especially in the sigmoid flexure Perforation has occurred in the rectum and in the jejunum After perforation local or general peritonitis develops In rare instances a peritonitis may develop without perforation

Mesenteric Lymph Nodes — Hyperemia and hyperplasia of the mesenteric nodes develop synchronously with the involvement of the Peyer s patches These nodes may reach the size of a walnut and often show necrotic areas They may suppurate rupture and give rise to peritonitis As a rule, the nodes about the lower end of the ileum show the highest degree of involvement

Spleen — The spleen usually is enlarged about three times its normal size It is soft, hyperemic and may show lymphoid hyperplasia and necrotic areas In rare instances an abscess may develop Typhoid bacilli may be demonstrated in properly prepared sections Spontaneous rupture of the spleen is an infrequent accident

Liver and Biliary Tract — The liver may show inflammation parenchymatous degeneration and areas of focal necrosis Small granulomas of macrophages and necrotic cells in hepatic lobules the so-called typhoid nodules are characteristic of typhoid Abscess of the liver is rare Acute yellow atrophy has been reported as a sequel

Acute cholecystitis may occur in typhoid the mural infiltrate consisting of mononuclear cells Secondary lymphoid follicles are often present and ulcers and perforation have been reported in the gall bladder Ulceration has been observed also in the common bile duct

Urinary Tract — The kidney microscopically may show cloudy swelling with granular degeneration especially in the cortex In rare instances there may be acute nephritis or pyelonephritis Multiple abscesses of the kidney occur Although large numbers of typhoid bacilli pass through the kidney pyelitis is rare Considering the frequency of bacilluria cystitis is uncommon The bladder mucosa often is hyperemic

Cardiovascular Apparatus — Cardiac lesions in typhoid are confined chiefly to the myocardium Endocarditis pericarditis and pancarditis are rare The former may be due to the typhoid bacillus but more frequently to some complicating secondary infection When death occurs early in the course of typhoid

the heart muscle seldom shows any change Later in the disease it is very apt to be flabby and in sections may show a peculiar mottled yellowish brown color due to fatty degeneration Small hemorrhages are noted frequently and in a few instances grayish or yellowish areas of infiltration or degeneration

Arterial changes similar to those observed in other acute infections have been observed There is apparently a tendency to involve the coronary arteries Degenerative changes may affect the intima or the media Thrombophlebitis with changes in the walls of the veins is observed frequently

Upper Respiratory Tract — Ulceration of the larynx has been observed in 20 to 25 per cent of necropsies and probably is due to invasion of the lymph follicles The ulceration often extends deep involving the cartilage causing necrosis and abscess formation

The Lung — Changes in the lung are common in typhoid at necropsy Pneumonia was present in 34 of 105 necropsies in one series of necropsies at the Johns Hopkins Hospital[4] and in 8 per cent of 2 000 autopsies at Munich[1] Occasionally the typhoid bacillus especially *B paratyphosus* B gives rise to specific forms of *pneumonia*[5] Lung abscess as a complication of pneumonia or of metastatic origin is rare It may follow one of the various forms of pneumonia or arise from aspiration of infected material especially from ulceration in the larynx Massive necrosis may occur Lung infarct due to an embolus from thrombophlebitis is quite common Deaths from pulmonary embolus may occur Primary typhoid pleuritis is rare Empyema may develop

Nervous System — Meningitis and brain abscess due to the typhoid bacillus have been demonstrated[39] Histologically the reaction consists of lymphocytic cells and macrophages The spinal cord and peripheral nerves rarely show any pathological changes

Voluntary muscles especially of the diaphragm the rectus abdominis and thighs often show non specific Zenker s degeneration

Paratyphoid C fever and sometimes the paratyphoids A and B differ pathologically from typhoid When they are primarily septicemic Peyer s patches are not involved and intestinal ulceration does not occur Instead there may be extensive fatty changes in the liver and subcapsular hemorrhages There may be pyarthrosis and specific pneumonia

Pathogenesis

Typhoid bacilli enter the mouth and in the majority of persons pass through the gastrointestinal tract to be killed or excreted without causing any trouble In susceptible persons the bacilli presumably invade the tissues cells and lymphatics of the oropharynx or esophagus but especially of the small intestine where for a time they may or may not cause lesions They are carried to the mesenteric

necrotic areas become hyperemic and hemorrhagic infiltration may occur Gradually the cellular elements in the periphery proliferate and extend over the denuded area until the original continuity of the epithelium is restored When ulceration is extensive, restoration may be incomplete so that the floor of the ulcer is covered with connective tissue containing few or no glandular elements Healed ulcers often may be recognized by their smooth pigmented surface, often depressed below the surrounding mucosa

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certain instances patients with severe attacks continue to be ambulatory, having what is called ' walking typhoid which often is fatal

Undesirable names were used in the past to designate typhoid or the para typhoids when the brunt of the attack is borne by or manifested in unusual areas as for example pneumotyphoid when the lungs are involved, meningo typhoid with specific meningitis and nephrotyphoid or renal typhoid The author reported a case of the latter in which the clinical picture was that of acute pyelonephritis[31] Typhoid in many of its unusual manifestations is described in detail in the works of Posselt[30] and of Hare and Beardsley[4] Typhoid in infants is difficult to diagnose and probably occurs more often than is believed It is described on a later page Typhoid may coexist with, and be modified by tuberculosis syphilis malaria, the dysenteries kala azar and other infections or other chronic diseases A rare afebrile form of typhoid has been observed

Symptoms and Signs

Onset and First Week — As a rule several days or a week pass after a patient first notices something awry before medical aid is sought Indisposition tiredness and irritability come on so gradually as to be ignored at first until they persist and increase in intensity during several days accompanied by fever anorexia headache general aching chilliness and lack of endurance Sleep often is dis turbed by dreams Uncomfortable warmth or actual fever and anorexia are among the most common early symptoms Headache usually is dull and constant Chilliness at first or in repeated bouts occurs more often than a single rigor at the onset Constipation or diarrhea may be noted Nosebleed occurs in 10 per cent of patients especially in children The relative frequency of early symptoms in a series of 237 cases[11] was as follows

Fever	237	Cough	85	Chill	50
Anorexia	148	Diarrhea	81	Vomiting	47
Malaise	133	Chill ness	80	Nausea	46
Headache	118	Dizziness	68	Epistaxis	28
Constipation	96	Abdominal pain	64		

Obviously the symptoms listed in the table are common to many acute in fections and typhoid often is not suspected unless it is present in the community or is kept in mind More common disea es usually are considered first such as influenza or viral pneumonia when there is evidence early of bronchitis with cough and chills Appendicitis is suspected when abdominal pain nausea and vomiting are prominent An onset with nervous and mental symptoms may suggest meningitis or encephalitis

Some patients may have various combinations of the symptoms listed in the table and recover after a few days with no further difficulty, but in more severe

nodes which may become swollen before visible changes occur in the intestine According to Goodpasture [1] and Adams[9] typhoid bacilli enter the plasma cells and macrophages of lymphoid tissue and live intracellularly in their original form or in changed form This may account for their localization in areas rich in these cells as in the intestine, spleen and bone marrow Parasitized plasma cells thus may serve as residual foci or transporters of infection

During the period of invasion, comprising the "incubation" period lasting from 3 to 14 days there are often no symptoms The onset of disease or reaction to infection presumably dates from the time the bacilli are disseminated from the original Peyer s patch mesenteric lymph node complex which constitutes the primary focus From this focus or from other foci in the biliary tract and else where bacilli escape into the blood directly or by way of the thoracic duct and are disseminated by the blood throughout the body giving rise to bacteremia and metastatic foci Relapses are due to the reactivation of the primary focus or to the spread of infection to new areas The symptoms of typhoid appear to be caused by the toxic products formed from injured tissue and from the hypothetic typhotoxin liberated by the disintegration of bacilli

The *incubation period* is variable but it usually lasts from 3 to 14 or more days from the time bacilli enter the body In a food borne epidemic studied by Sawyer[33] one person became sick on the third day 12 on the fifth and 19 on the sixth day The length of the incubation period depends on the number of bacilli ingested and on the resistance of the victim Carriers may develop the disease at any time

Predisposing Factors — Malnutrition, starvation, gastrointestinal derange ments from dietary indiscretion excesses and minor infections exposure and exhaustion may all favor invasion of typhoid bacilli It has been noticed fre quently that recent arrivals in a city are more susceptible to typhoid than old residents They may however have contracted typhoid before arrival New recruits in an army seem to be more liable to contract typhoid than seasoned troops probably because of lowered resistance due to unaccustomed hardships fatigue and change of diet

Clinical Varieties of Typhoid and Paratyphoid

All gradations of severity and all combinations of signs and symptoms occur A few patients may remain ambulatory with but slight discomfort often mistaken for an attack of grip, some with mild infections may be sick in bed for a few days to a week those with moderately severe or severe attacks lasting several weeks usually are regarded as having "typical typhoid in a few disease may last for many months either continuously or in repeated relapses and in rare cases a rapidly fulminating form occurs which ends fatally in a few days In

necrosis the temperature rises until it reaches its height early in the second week the patient becomes sicker drowsier or delirious the spleen becomes palpable rose spots appear and the pulse may be slow Abdominal distention occurs and there may be constipation or diarrhea Constipation is more common than diarrhea and is noted in from 40[11] to 50 per cent[6] of patients Diarrhea occurs

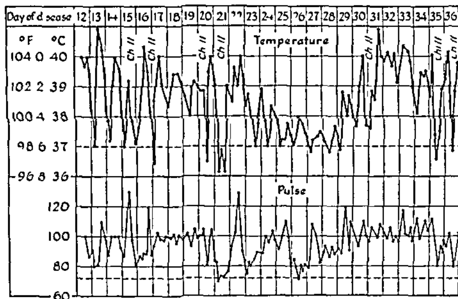


FIG 8 Irregular remittent fever with repeated chills a remission of several days and a relapse with similar irregular remittent fever in a portion of a chart of typhoid lasting 45 days The patient a woman aged 49 ate clams early in September She first noted weakness about September 16 and 4 days later was surprised to find that her temperature was 39 5 C (103 F) Three days after this there were chills epigastric pain cough and headache She entered the hospital on the twelfth day She did not seem very sick and viral pneumonia was suspected During the disease repeated chill sweats and fluctuation of fever were prominent the spleen became palpable and malaria was suspected A persistently normal leucocyte count relative bradycardia and a relapse suggested typhoid but repeated cultures of the blood stool urine and sternal marrow were negative until *E typhosa* was isolated from the feces on the thirty-eighth day The Widal reaction rose slowly to low undiagnostic titer of 1 80 Convalescence was uneventful

in 17[6] to 35 per cent[41] Diarrhea may occur at any time and may be among the first symptoms It may alternate with periods of constipation In the severest cases delirium or drowsiness may pass soon into stupor Nursing care and feeding become difficult Stools and urine may be passed involuntarily The course may be punctuated by repeated collapses of the circulatory system Shaking chills and drenching sweats may recur (Fig 8) The fever usually is continuously at a high level and the pulse rate relatively slow A certain number

cases there is no abatement The fever rises higher each day (Fig 7), and the symptoms deepen during the first week in proportion to the intensity and progression of the lesions in the intestine or elsewhere, until the seriousness of the disease becomes evident Bacteremia is almost always present The patient finally is obliged to remain in bed and shows evidence of profound infection and

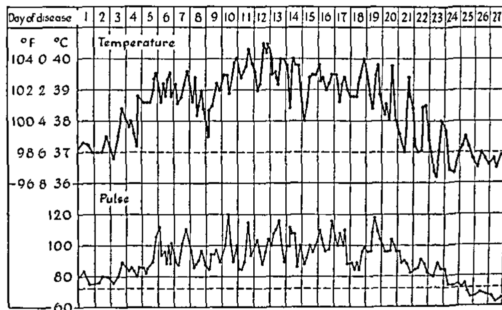


FIG 7 A so-called typical fever chart of typhoid of 25 day duration The patient a Chinese woman aged 20 entered the Chungking Central Hospital in August 1945 for an appendectomy A normal appendix was found Seven days later a slight fever appeared but was disregarded In the next 2 days the fever rose higher and the patient had headache and transient attacks of abdominal pain The leucocytes numbered 7 000 per cu mm and 2 days later 3 000 averaging 5 000 throughout the disease The pharynx was slightly injected the spleen was palpable and slight sweating occurred frequently Despite the high fever the patient was never drowsy and did not seem to be seriously sick Malaria was strongly suspected but there was no response to quinine A crop of rose spots appeared on the chest and back on the fifteenth day and again on the eighteenth Repeated cultures of the blood urine and stool did not show typhoid bacilli The Widal test was repeatedly negative until a titer of 1 320 for typhoid H agglutinin appeared on the twentieth day The diagnosis was proved by cultivating *E typhosa* from aspirated sternal marrow on the twenty second day (Courtesy of Dr H C Kao)

Note the gradual rise of fever in the early period its decline on the eighth day the subsequent high levels with slight remissions and finally the lytic decline with deep remissions and each peak lower There is average relative bradycardia

toxemia' As the severe stage is approached during the second week, the face becomes flushed the tongue more coated apathy or drowsiness appears and the lips and skin are hot and dry although sweating may occur

Severe Stage — With involvement of more lymphoid tissue and beginning

Hydrotherapy often causes a temporary lowering of fever When healing of the ulcers and recovery begin the fever gradually declines steadily or in daily steplike fashion over a week or more or in deep swings (Fig 7) until the normal is reached It may fall suddenly by crisis or rapid lysis It may then become subnormal for a while The persistence of low fever may indicate continued disease or complication with perhaps some other disease The temperature after having followed its course may diminish somewhat for several days and rise again to high levels (Fig 8) as infection recurs or spreads to new areas in the intestine or elsewhere It may on the other hand become normal remain so for several days to two weeks and rise again slightly as a recrudescence of a day or more or to high levels during a relapse Relapse or relapses may be milder or more severe than the primary attack

Pulse —One of the most suggestive diagnostic signs of typhoid is the relatively slow pulse rate as compared with the temperature (Figs 7 and 8) McCrae[8] reports 176 cases out of 500 in which the pulse rate did not reach 100 The cause of bradycardia is not clear The pulse rate however may be high in proportion to the fever or may fluctuate with large swings of temperature (Figs 7 and 8) When a patient with relative bradycardia suddenly develops a frequent pulse rate pneumonia perforation hemorrhage shock like circulatory failure or other occurrence should be suspected The development of severe bradycardia during defervescence or convalescence is suggestive of myocarditis or heart block During convalescence from typhoid as in other fevers the heart often is irritable physical exertion or emotional excitement giving rise to a transitory tachycardia This instability may persist for several weeks but has no special significance

The pulse wave may be dicrotic which has no significance other than indicating diminished peripheral resistance Among 30 patients [9] transitory electrocardiographic changes occurred in nearly half The heart itself unless previously injured seldom gives trouble in typhoid

Bronchitis may persist or develop during the course There may be laryngitis with aphonia or ulceration Esophagitis may occur

Blood Pressure —As a general rule the blood pressure falls slightly early in typhoid and continues below average during convalescence It is desirable to keep a daily charted record of blood pressure as certain serious occurrences at times affect it materially Hemorrhage of moderate degree may reduce blood pressure 20 to 30 mm of Hg There may be no change even with severe hemorrhage After perforation there may be a sharp rise or fall in blood pressure or no change at all Fall in blood pressure accompanies peripheral vasomotor collapse the serious shock like state of circulatory failure

Skin —*Roseola* —Toward the end of the first week and up to the third week of typhoid the characteristic rose spots appear in about 50 per cent of patients Thereafter they occur less often They are pink circular macules or papules

of patients with high fever may not appear to be proportionately sick as described in the legends of Figs 7 and 8 During this time bacteremia may persist agglutinin begins to develop in the blood, and bacilli appear more commonly than before in the stool and urine It is during the second and third weeks that hemorrhage and perforation occur most often Death usually occurs during this stage from "toxemia", circulatory failure, hemorrhage perforation or from complications In the majority of cases, after one to several weeks evidence of improvement slowly appears as the internal lesions stop progressing and begin to heal, leading to the stage of recovery

Stage of Recovery — In the "typical" case (Fig 7) resolution of the intestinal lesions begins in the third week and unless new areas are involved in a relapse, the clinical symptoms slowly abate The fever gradually falls, evidence of toxemia lessens the patient becomes rational, if previously confused and takes an interest in the surroundings, appetite returns and the spleen recedes The agglutinin titer may continue to rise but bacteria disappear from the blood and often from the stools The temperature may fall below normal in early convalescence Occasionally recovery occurs quickly by crisis or rapid lysis

Symptoms and Signs in Detail

Fever — The fever curve in typhoid is characteristic (Fig 7) in many but not in all cases (Fig 8) With improvement in diagnostic means many attacks of typhoid are now recognized which formerly were missed especially the mild forms of short duration and those with unusual courses Even in mild cases the fever curve may be a miniature of the severe type with a gradual increase in temperature, then a gradual decline to normal

The temperature curve usually shows a gradual step-like rise reaching the maximum in 7 to 10 days Fever usually is higher late in the day with a slight fall in the morning but each peak is higher Patients are rarely observed in the early period since medical aid usually is postponed until the seriousness of the disease is evident, Figure 7 represents the fever curve of a patient who developed typhoid in the hospital and consequently shows the beginning of fever After the fever reaches its height it remains fairly constant between 39° C (102° F) and 40 5° C (105° F) for a week or two, while necrosis and ulceration take place In some patients it may not exceed 39° C (102 F) and in others it may hover near 41° C (106° F) or more The fever generally is classified as the high continuous type In a small proportion of cases it may be remittent with chills fluctuating daily between normal and high levels or alternating with the continuous form In others it may be completely irregular (Fig 8) In rare instances the temperature may seldom rise above normal Sudden changes of temperature which has been constant may signify hemorrhage perforation or vasomotor collapse

is noticed first during early convalescence The patients can be assured that they will regain their hair Transverse grooves on the nails are common In rare cases both finger and toe nails may be lost

Sweating — Sweating is not so characteristic of typhoid as of certain other infections but it may occur Repeated chills and severe sweats may follow sudden drops in temperature (Fig 8) Sweating may herald certain accidents like hemorrhage or perforation or the onset of complicating pyogenic infections

Mouth — The lips usually are dry and cracked The lips teeth and gums may be become covered by sordes if not cared for The tongue early in the disease usually is moist and covered with a thick grayish coat Stomatitis and gingivitis occur

Abdomen — Even early in the disease there is apt to be moderate distention which may become severe later in the form of tympanites There is often tenderness and gurgling on pressure in the right lower quadrant Since the substitution of a reasonably full diet for one composed almost entirely of milk distention of the abdomen has been much less troublesome Pain in the abdomen may be one of the early symptoms Moderate abdominal pain is present in about 50 per cent of patients at some time during the course of the disease It is due most frequently to gas Sudden severe pain and/or rigidity may occur with perforation

Spleen — The spleen is enlarged in practically all cases and palpable in from 50 to 75 per cent of patients according to the different observers In few of the acute infectious diseases is the spleen so uniformly swollen as in typhoid which makes it of considerable diagnostic value except in regions where malaria and kala azar occur It swell during the first week and reaches its largest size during the second and third week Usually it is soft and sometimes tender During defervescence it returns to its normal size The spleen may be palpable in mild attacks and not in severe ones and its size has no relation to the severity of the attack It is difficult to feel in patients with thick abdominal walls or in the presence of tympanites Fibrosis of the spleen from previous disease may prevent its enlargement during typhoid

Liver — Hepatitis and jaundice occur at times

Nervous System — Headache is one of the most common symptoms It may mark the onset There is nothing in the location or character of the pain which is typical of typhoid It is usually dull and often continuous The frequency of drowsiness or somnolence during the disease was responsible for the name typhoid Occasionally however insomnia and restlessness occur Delirium is common particularly in severe attacks in alcoholics and especially at night It is usually mild and accompanied by twitching of muscles purposeless movements muttering mild delusions hallucinations and disturbed sleep At times there may be severe mania with violence These psychic disturbances are almost always transitory and disappear with recovery but they may develop during convales

standing out as a rule distinctly on the white skin but difficult to detect in the negro Their average diameter is 2 to 3 mm They fade on pressure As a rule, 5 to 10 spots are present In exceptional cases, however, they may be much more numerous They often are found mostly on the abdomen and chest, next on the back and occasionally on the extremities and the face In some cases they are present only on the extremities McCrae[6] stated that spots were found in 93 2 per cent of the white patients and 20 6 per cent of the colored at some time during the disease He also reported cases in which the spots did not appear until late or even after the temperature had become normal The abundance of rose spots is not an index of the severity of the infection Rose spots appear characteristically in crops The average duraton of a single crop is 3 to 5 days although they may persist longer As they fade away they often leave a faintly pigmented spot In some instances there is a single crop, in others several successive ones The interval between crops is variable In order to differentiate rose spots from other blemishes they should be circled with indelible ink and observed for several days Their cause is unknown Some believe they result from thrombi or other injury to capillaries Typhoid bacilli may be present in the lymphatic spaces in the reddened area

In severe infections *purpuric spots* may appear with or without thrombopenia, probably as a result of injury to the walls of the capillaries

Sudamina — This condition is found more frequently in typhoid than in the other infectious diseases and usually appears in the second or third week mostly over the flanks and abdomen There occur vesicles containing watery fluid and varying from 1 to 2 mm in diameter They may itch and tend to coalesce

Herpes — Herpetic eruptions are so rare in typhoid that the presence of herpes speaks against typhoid When present herpes usually appear during the first week It occurs commonly in the paratyphoids

Furuncles — These are quite frequent and troublesome They usually appear on the back especially on the buttocks and elsewhere They are more apt to occur in debilitated patients late in the course of the disease Cultures show the presence in them of staphylococci or hemolytic streptococci At times deep *abscesses*, especially in the buttocks may account for an unexplained rise in temperature during early convalescence

Bed Sores — These appear especially in patients with involuntary urination or defecation or when there is improper care of the skin Most frequently they occur in the sacral or gluteal region rarely on the heel, elbow or over the scapulas Bed sores usually are the result of pressure necrosis

Hair and Nails — Some loss of scalp hair almost always follows a severe attack of typhoid The beard and axillary and pubic hair are involved rarely Curschmann reported 2 cases of complete alopecia The falling of the hair usually

Paratyphoid was of especial importance during mobilization of the U S Army in 1916 along the Mexican Border[7] The mortality rate in the Army from paratyphoid A was 2 3 per cent and from paratyphoid B 5 per cent Little is known clinically of paratyphoid C

In individual cases typhoid and paratyphoid are clinically indistinguishable but a few characteristics of paratyphoid may be mentioned The incubation period often is shorter and the onset may be more abrupt with a chill, abdominal pain and vomiting Herpes are said to occur in 5 to 10 per cent of cases and a morbilliform eruption occurs In a few patients examined sigmoidoscopically there was a moderate degree of lymphoidal hyperplasia of the mucosa and in several instances small round ulcers were distributed evenly in the lymphoid prominences[33( )] Since the course generally is mild there are fewer complications and a lower mortality rate The only certain way of differentiation rests on the identification of the causative bacillus[5( )] The demonstration of the rise in titer of specific agglutinins is helpful but less reliable

Paratyphoid C — Paratyphoid C differs more from the prototype typhoid than the paratyphoids A and B It occurs sporadically in Asia but a few cases have been reported in England In 9 cases studied by Wasti[37( )] the disease seemed to be primarily a septicemia with a sudden onset and remittent fever lasting a week or two Pneumonia and suppurative arthritis were common Diagnosis is made principally by blood cultures the stools seldom contain the bacilli since intestinal lesions do not occur

RELAPSE

In 10 to 15 per cent of typhoid patients temporary improvement or remission with a decline of fever during the disease is followed by rise in fever and reappearance of symptoms (Fig 8) or the temperature becomes normal and recovery seems established for several days to a week or more when the disease recurs in its usual form as a relapse Several relapses may recur irregularly and prolong the disease over many months As a rule relapses are not so severe as the primary attack but they may be more so In them hemorrhage and perforation occur less often and the mortality rate is lower Relapse bears no relation to the severity of the first attack and may be precipitated by indiscretions of diet overactivity or other causes or it may occur without obvious reason in well managed patients

Relapses indicate that infection persists and either reinvolves the areas previously attacked or results from the invasion of new ones Second attacks of typhoid which may occur as long as 50 years after the first one in carriers may in this sense be regarded also as relapses but in most cases perhaps second or third attacks at long intervals are caused by reinfection from outside sources

cence Permanent mental derangement is rare after typhoid Curshmann stated that in 4 000 cases of typhoid psychoses developed in 42 during the febrile period Only 2 of these persisted beyond the period of convalescence and 1 of these recovered in 6 months the other in 9 months Mental depression and melancholia may also occur Infants and children may have convulsions usually at the onset of disease

Peripheral neuritis and polyneuritis may develop during or after the attack Acute meningitis caused by *E typhosa* is rare[39] Encephalitic symptoms occur

Body Weight — Coleman[16] has shown that by proper feeding it is possible for a patient to pass through typhoid without loss of weight Even under a liberal diet however most patients lose considerably in weight especially in the severe cases when delirium or other factors interfere with feeding

Typhoid in Infants and Children

The symptoms of typhoid in infants vary somewhat from those in adults[14, 15, 38] Vomiting and convulsions as initial symptoms are frequent Nervous features especially meningeal symptoms are more common Since the intestinal lesions usually are less severe than in adults or are absent, hemorrhage and perforation are infrequent The mortality rate is high In one series of 105 infants less than a year old 77 died (Weech) Serious sequels as deaf mutism and arrested mental development are reported Typhoid in childhood resembles that in adults except that usually it is milder Abdominal pain occurs more often at the onset The pulse rate and leucocyte count are often higher than in adults The mortality rate in one series of 14 children under the age of 12 was 6 per cent

The Paratyphoids

In general the paratyphoids resemble typhoid so closely that clinical differentiation is impossible They must however, be dealt with as separate entities in regard to epidemiological control prognosis and specific prophylaxis As a rule, the paratyphoids are much less common less severe and the mortality rate lower than typhoid in the United States An outbreak of 51 cases of paratyphoid B was reported recently from England[24] In China paratyphoid is relatively more common and in one series of cases[41] there were 256 cases of typhoid, 48 of paratyphoid A and 17 of paratyphoid B The ratio was higher in children under 12, and in one series paratyphoid A and paratyphoid B together comprised 37 per cent of 411 cases of typhoid paratyphoid[14] In a group of 83 patients in South America[3] 71 had typhoid 10 paratyphoid, and in 2 both typhoid and paratyphoid bacilli were present

found at necropsy The most frequent site is in the lower ileum but it may occur in the appendix or in any portion of the large bowel including the rectum The statistics of Liebermeister[6] show perforation in the ileum in 4,4 the colon in 55 appendix in 32 Meckel s diverticulum in 4 and the jejunum in 4 Perforation occurs during the period of ulceration toward the end of the second week and after Rarely does it appear early as is observed occasionally with hemorrhage In another series[3] of 39 cases perforation occurred in the second week in 10 third week in 1 fourth week in 7 fifth week in 5 sixth week in 1 seventh week in 2 eighth week in 1 In 10 the perforation occurred after the patient was well enough to be out of bed the latest was on the fiftieth day As a rule the late perforations are found in prolonged attacks with relapses The immediate de termining cause of the perforation varies Sixteen out of 30 perforations in the Johns Hopkins series[3] had diarrhea at the time of perforation Distention is also an important cause Other factors are straining at stool constipation vomiting and unusual physical exertion Often no cause is evident the ulcer simply penetrates the bowel wall

The incidence of perforation in typhoid varies in different studies from 1 to 6 per cent averaging about 3 per cent Perforation is relatively infrequent in children It is rare under 10 years of age The mortality rate is extremely high almost all are fatal unless treated promptly by surgical method even then the rate is over 60 per cent Perforation accounts for 15 to o per cent of typhoid deaths

Occasionally warning symptoms of perforation occur from a slow progression of areas of ulceration and of local peritonitis Usually the onset is sudden with sharp abdominal pain Initial pain rarely is absent in patients whose mental condition is fairly normal It may be obscured in the delirious or apathetic patient The pain may be constant or paroxysmal in character with intervals of almost complete freedom Pain usually is widespread in the abdomen and may be intense In about 25 per cent of cases it is referred to the right lower quadrant and acute appendicitis is suspected When the pain is in the right upper quadrant cholecystitis is suspected The pain grows progressively worse and often is increased by breathing or movement as turning in bed

Sudden abdominal pain is the most important early symptom All other signs symptoms and laboratory data are more inconstant and cannot be relied upon in the early period when diagnosis is so important In rare cases there may be little or no early evidence of pe foration If there is a transitory shock like state depending upon the degree and suddenness of perforation the pulse rate may increase and the temperature may fall but no change in these at all is common Changes in the blood pressure and leucocyte count also are inconstant they may rise or fall or be unchanged A sudden change in either direction in any of the factors mentioned together with other new symptoms is significant

Serious Occurrences During Typhoid

Complications imply more or less unrelated diseases or conditions superimposed upon or concurrent with typhoid Hemorrhage and perforation are not complications but characteristic features of typhoid The bacteremic nature of typhoid accounts for the involvement of other organs and tissues as well, all to be included in the clinical picture

Hemorrhage

Bleeding of slight degree from the sloughing ulcers occurs at times in most severe attacks and may be detected only by chemical tests Significant bleeding with gross blood in the stool occurs in 5 to 8 per cent of typhoids The amount lost varies greatly but may lead to exsanguination and early death A single hemorrhage or repeated ones may occur Hemorrhage usually occurs during the second and third weeks from the oozing of many areas, or when large vessels are eroded by the ulcerative process Hemorrhage may be the first evidence of disease in the rare 'walking typhoid" and may provide the first clue to diagnosis in established attacks There is no relation between hemorrhage and the severity of typhoid It may occur during convalescence

The passage of a bright red or a tarry sticky stool may be the first evidence of gradual bleeding of moderate amount The sudden loss of large amounts sometimes as much as a liter or more, usually causes striking but variable changes in the clinical course There may be signs of collapse with rapid feeble pulse a decrease of fever and blood pressure pallor faintness, apprehension chilliness sweating and cold damp skin Pain is absent Hours or even days may elapse after bleeding in the bowel before blood is passed through the anus Care must be taken not to confuse intestinal hemorrhage with bleeding hemorrhoids After a large hemorrhage there is usually no immediate diminution in the number of erythrocytes nor in the measured amount of hemoglobin until the intravascular volume of blood is replaced and diluted with tissue fluid The red cell count may diminish in an hour or not for 48 hours depending upon the degree of hydration of the patient and on other factors A diminution usually appears in 4 to 8 hours Change in the leucocyte count is variable The prognosis when hemorrhage occurs is uncertain since it is impossible to know when bleeding will stop The mortality rate among typhoid patients with hemorrhage is about 25 per cent It is probably considerably less at present with improvements in the technic of transfusion

Perforation

The most serious incident of typhoid is intestinal perforation The perforation usually is single rarely multiple As many as twenty five perforations have been

cause is unknown but it is believed to be the result of a "toxic" action on the central nervous system or on the peripheral vessels It does not necessarily involve the heart itself The condition is apt to occur during the height of the disease or during defervescence and may even occur in convalescence It may come gradually or suddenly without warning often for no perceptible reason and is manifested by a rapid fall of the fever sometimes to subnormal levels a fall in blood pressure a rapid and feeble pulse cold skin sweating dyspnea and apprehension or coma Pulmonary edema may appear Circulatory collapse often accompanies or follows severe chills

Thrombosis

The frequency of recognized thrombosis varies widely ranging from 1 to 12 per cent in different reported groups of cases A fair average incidence is 5 per cent Unrecognized thrombosis probably is much more frequent It may give rise to sudden unexplained elevations in temperature during the course of typhoid or afterward Some of the pulmonary symptoms and other obscure complaints observed during the later course of typhoid are due to emboli from thrombosed veins Thrombosis occurs most frequently in the femoral veins 5 times more frequently in the left than in the right Thayer in an analysis of 42 cases reported the following distribution femoral 21 times popliteal 5 veins of calf 5 internal saphenous vein 3 pulmonary artery 1 pulmonary and common iliac vein 1 axillary vein 1 It probably results from phlebitis stasis of the blood and a change in the composition of the blood

Thrombosis develops most frequently from the third week on about half the cases occurring in the third or fourth week In about 30 per cent of cases thrombosis appears during convalescence As a rule the onset is accompanied by pain and tenderness in the region involved If the iliac veins are involved abdominal pain might be mistaken for perforation Chills accompany precede or follow the other clinical evidence of thrombosis in 30 per cent of the cases Repeated chills are not unusual Fever almost always occurs

In case the thrombosed vessel is accessible it may be readily palpated When in the femoral vessel pain or tenderness appears along the course of the vein In case the vessel involved is in an extremity edema practically always develops its extent dependent upon the size of the vein and the degree of occlusion The accessory veins become dilated and may become varicosed later Leucocytosis *is present in about half of the cases and may reach 25 000 In rare instances the* leucopenia present in typhoid is not affected by thrombosis Emboli may become detached and lodge in the lung giving rise to the characteristic symptoms of a pulmonary embolus Venous thrombosis rarely is a dangerous complication except for pulmonary embolism Recovery usually is complete but there may

A steady increase of leucocytes is suggestive of perforation but may occur with cholecystitis There may also be retching or vomiting, both of which are rare in typhoid and hiccough Localized or general rigidity and tenderness may appear early Distention and tympanites may appear immediately from escape of gas or fluid into the peritoneal cavity It may be impossible without roentgenography to differentiate gas in the intestine which often precedes perforation, from gas in the peritoneal cavity Obliteration of liver dulness is of little aid in diagnosis It is often difficult to distinguish between intestinal perforation, rupture of a mesenteric lymph node acute cholecystitis and appendicitis all of which occur in typhoid It is also difficult to detect perforation in stuporous or comatose patients Roentgenographic evidence of air free in abdominal cavity is an important aid in diagnosis in doubtful cases

In the later stages the usual evidence of general or local peritonitis develops slowly or quickly There may or may not be nausea, vomiting chills distention, rigidity pain tenderness paralytic ileus, a shock like state with lower temperature coldness sweating faster pulse and respiration rate and an increase in the leucocyte count Peritonitis may occur without perforation

In conclusion it may be said that the symptomatology of perforation in typhoid often is confusing The diagnosis must be made by weighing the evidence and constantly remembering that many of the symptoms only appear after general peritonitis has developed, to save life one cannot await the appearance of these manifestations In order to resort to surgical measures sufficiently early to make the chances of recovery good an operation usually must be recommended on the basis of the probable diagnosis of perforation To delay operation until even the inexperienced could make the diagnosis removes the chance of recovery Better an operation where no perforation is found than to delay until surgical measures, while confirming the diagnosis cannot save life

In making the differential diagnosis the possibility of acute appendicitis may have to be considered but as this too requires surgical measures no delay should intervene in advising operation Acute cholecystitis may present many of the symptoms of perforation The evidence of shock is less and the tenderness is localized in the right upper quadrant Surgical intervention rarely is required in acute cholecystitis complicating typhoid Pneumonia with pain referred to the abdomen may simulate perforation A careful examination of the lower chest must be made In doubtful cases a roentgenogram of the chest is of value Thrombosis of the iliac vein may give rise to acute abdominal pain chill and leucocytosis

Circulatory Collapse

Collapse of the peripheral circulatory system or a shock like state occurs in typhoid as in other infectious diseases and is an important cause of death Its

length of time surgical interference may be advisable The majority of attacks however are only moderately severe and subside within a few days

Hepatitis and *jaundice* may occur without cholecystitis

Nervous and Mental Disturbances

In addition to the ordinary nervous and mental symptoms so common in typhoid there are some unusual disturbances Actual meningitis may develop[39] The symptomatology does not present any special feature Spinal puncture is necessary for diagnosis The purulent spinal fluid may contain typhoid bacilli alone or complicating pyogenic cocci Hemorrhage thrombosis embolism encephalitis and brain abscess are infrequent complications The symptomatology is that observed in similar processes from other causes Pure cultures of typhoid bacilli have been isolated from abscesses of the brain Aphasia without evidence of paralysis has been observed This is thought to be of cortical origin and the prognosis is good Acute myelitis with paraplegia has been noted Bulbar symptoms also have been reported

Peripheral neuritis is not infrequent in typhoid Some of the reported paraplegias have been of this origin Tender toes usually have been considered as a manifestation of neuritis

Other Occurrences and Complications

Parotitis — Parotitis at one time developed in 1 per cent of all patients with good oral care it rarely occurs in modern times It is usually unilateral but may be bilateral both glands being involved synchronously or successively It usually develops at the height of the disease and is more frequent in severe attacks Clinically the symptoms are those observed with parotitis from other causes As a rule the process is nonsuppurative The typhoid bacillus may be found in pure culture in the infected gland or together with complicating pyogenic cocci Infections may be hematogenous or by way of Stenson s duct Thrombosis of the jugular vein may be one of the serious consequences

Thyroiditis — Acute thyroiditis usually involving only one lobe is a rare complication of typhoid It is reported to develop more frequently when there is a previously enlarged thyroid It is claimed that this complication is more frequent in typhoid fever in Switzerland where struma also is common

Orchitis — Involvement of the testicle in typhoid is rare It appeared 4 times in 1 500 cases in the Johns Hopkins Hospital series The process usually begins as an orchitis and remains confined to the testis or may involve secondarily the epididymis Rarely is the epididymis first infected The trouble usually appears late with a chill followed rapidly by pain and swelling of the testicle Beardsley reports that 71 of 10 recorded instances developed during conva

be permanent edema, varices ulcers, cramps and paresthesia in the involved extremity

Thrombosis of arteries is comparatively rare, occurring in 4 of the 1 500 cases of the Johns Hopkins Hospital series[8] 1 in the middle cerebral, 2 in the femoral and 1 in the brachial artery

Gangrene may occur as a result of arterial thrombosis especially in the legs Areas of necrosis may involve the skin anywhere and other parts of the body as well Necrosis of the uvula has been reported

Cholecystitis

The gallbladder is the most important metastatic focus in the body The bile which has antagonistic action on many bacteria is favorable for the growth of the typhoid bacillus Typhoid bacilli probably are present in the gallbladder in every case of typhoid The chief channel through which the bacilli reach the gallbladder is through the biliary ducts in the liver Many of the typhoid bacilli in the stools reach the intestine through the biliary tract In case the drainage from the gallbladder is not good, cholecystitis may develop in which the typhoid bacillus plays the chief role There may be ulceration and at times perforation

Cholecystitis was recorded in only 1 2 per cent of the Johns Hopkins Hospital series[5] Careful observation will show its presence more frequently than is generally suspected It may occur at any age even in infants The time of its appearance varies greatly It may appear early in the second week, be delayed until convalescence or the first clinical manifestation may appear months or years after recovery Gallstones frequently develop as a result of typhoid, and bacilli may reside in the gallbladder for years In Botsford s case cholecystitis occurred 43 years after typhoid

The onset may be gradual or sudden When the onset is sudden, general abdominal tenderness and rigidity may render diagnosis difficult or impossible The symptoms may be readily mistaken for perforation When the onset is gradual pain and tenderness are localized over the gallbladder Chill and vomiting at the onset are not unusual The pulse and respiration rate are increased The leucocyte count may reach 10,000 to 15,000, rarely higher Jaundice develops in about 30 per cent of the cases The gallbladder may be palpated if it is distended

The progress of the condition is variable Perforation may occur Eleven of a series of 39 patients were operated upon with a mortality of 5 6 per cent All patients with perforation not treated surgically died Ashhurst collected 21 cases of acute typhoid cholecystitis operated upon with a mortality of 61 9 per cent These figures indicate that cholecystitis requires careful watching When the symptoms are intense and do not tend to subside within a reasonable

Pneumonia — Pneumonia develops in 2 to 3 per cent of patients It may occur either at the onset as tracheobronchopneumonia or more frequently later during the disease Pneumonia may be caused in rare cases by *E typhosa*[28] but in most instances it is a complication caused by other bacteria chiefly pneumococci hemolytic streptococci or staphylococci alone or in mixtures It may be of the lobar form if the pneumococcus is the cause or otherwise if other bacteria dominate The physical findings are those ordinarily observed for the respective forms Pneumonia more commonly occurs with the paratyphoid fevers and is caused by the respective bacilli

Pulmonary abscess and *necrosis* are rare complications and most frequently arise from an infected embolus from aspiration or as metastatic phenomena in a general pyemia

Pleuritis and *empyema* may occur caused by *E typhosa* or as a complication with other bacteria They are not common in typhoid

Endocarditis is a rare complication of typhoid The mitral and aortic valves are involved most frequently Typhoid bacilli have been isolated from the valves, but other bacteria such as staphylococci or streptococci are found more commonly The signs and symptoms are those ordinarily found in this condition Murmurs apparently not caused by valvular lesions appear during typhoid and disappear after recovery They are probably of 'hemic or myocardial origin

Pericarditis is even more infrequent than endocarditis It may be due either to the typhoid bacillus or to pyogenic microorganisms It may develop at any time It may be fibrinous serous or even purulent

Myocarditis — Involvement of the myocardium is rarely of importance in typhoid[9] Although changes in the coronary arteries occur during typhoid clinical evidence of coronary disease is rare The physician s attention may be attracted to myocardial weakness by lowered blood pressure edema of the feet pulmonary râles or by slight dyspnea during convalescence Bradycardia tachycardia or arrhythmia may be noted A frequent pulse with or without arrhythmia and with dilatation of the heart may be the first and only clinical manifestation Occasionally there is a mitral murmur with accentuation of the second pulmonic tone The heart tones may be faint The prognosis is favorable Unless the heart was previously injured symptoms of cardiac incompetence are rare Circulatory failure is of far greater importance than heart failure in typhoid

Nephritis — Febrile albuminuria is common in typhoid but nephritis with blood or casts is not As a rule renal complications appear during the height of the disease but may develop during convalescence The clinical manifestations of nephritis are limited to the urinary findings Rarely are there edema or uremic symptoms Mild forms subside rapidly In the severe forms with casts and blood in the urine the prognosis is grave This form usually is found as a complica

lescence in 37 the right and in 27 the left gland alone was involved, in 3 it was bilateral In 43 both testis and epididymis were involved, in 31 the testis alone and in 10 the epididymis alone Suppuration occurred in 22 of the 102 cases There is no relation between the severity of the typhoid and the development of this complication The trouble subsides within 10 days to 2 weeks and is followed occasionally by atrophy of the testicle Here, as in involvement of other glandular tissues, the typhoid bacillus is found frequently either alone or with pyogenic cocci

Mastitis — This unusual complication of typhoid may develop in either sex, although more frequently in the female It usually appears late in the course of the disease and the onset may be marked by chill, fever and leucocytosis Suppuration often occurs and typhoid bacilli are present in the pus Mastitis is not a serious complication In some cases there may be pain in the breast without induration In this mild type the diagnosis of mastitis may be questionable

Pancreatitis — Hemorrhagic pancreatitis may accompany typhoid cholecystitis Its clinical recognition is difficult

Abscess of the Liver — The complications involving the liver are relatively infrequent Abscess rarely occurs The pus frequently but not always contains the typhoid bacillus In addition to the symptoms of sepsis there is pain in the hepatic region often increased on breathing In case the abscess is adjacent to the diaphragm pain on breathing may be referred to the neck or back Pressure or percussion over the right lower thoracic area may be painful Palpation of the liver may reveal tenderness In the absence of evidence of sepsis an abscess may be easily overlooked Suppurative pylephlebitis may be associated with thrombosis of the portal vein

Ulcers in Pharynx and Esophagus — Ulceration in the pharynx is unusual Ulcers in the esophagus were reported by Louis in 7 of 46 necropsies Other observers have found them rarely They are located usually near the cardiac end Frequently they do not cause symptoms, although at times there is dysphagia On healing they may give rise to stricture

Ulcers in Larynx — Ulceration of the larynx is present in 3 to 10 per cent of typhoid patients at necropsy The posterior wall at the insertion of the vocal cords is the most frequent site of the lesion The typhoid bacillus in pure culture may be obtained from the ulcer In the majority of cases the lesion develops after the third week and rarely is diagnosed clinically Some of the manifestations are hoarseness, aphonia, inspiratory stridor, dyspnea, metallic cough with blood tinged mucus and dysphagia There may be sudden edema with cyanosis with rapidly fatal termination Aspiration pneumonia or pulmonary abscess may develop as a complication The prognosis is grave Tracheotomy is advisable at the first appearance of obstruction Stenosis may develop as a result of the ulceration

Bones and Joints — Involvement of the bones and joints may develop during typhoid but more often afterward as sequels They are among the most distressing features of the disease Arthritis or destructive pyoarthritis may affect one or more joints and persist for months Spondylitis is especially serious Typhoid or paratyphoid bacilli may be present in the pus Healing may result in a destroyed or ankylosed joint

The typhoid spine a term used to describe pain in the lower thoracic or lumbar region often radiating around the body formerly was mistaken for a neurosis It is a spondylitis, which may follow even mild attacks and is more frequent in males There is often roentgenographic evidence of arthritis and in some cases of destruction of the vertebras [0]

The onset may be sudden like an acute lumbago or there may be a gradually increasing pain especially noticeable on movement In addition to radiating around the trunk it may extend into the lower extremities At times the spine is held rigid and bending becomes impossible There may be tenderness and paresthesia along the thoracic or lumbar nerves and spasm of the muscles they supply Pressure on the spinal cord may cause disturbance of the reflexes and persistent weakness of the legs Muscular atrophy of the legs kyphosis or scoliosis may develop Disturbances of the bladder and rectum have been noted in a few instances

In spite of the intense pain and rigidity complete or almost complete recovery may be expected in a few weeks or months but in some cases one or more years may elapse before restoration occurs

Periostitis is the most common lesion of bones and as stated may appear during an attack but usually as a sequel sometimes not for months or years after the primary disease It occurs in about 1 per cent of patients The ribs clavicles long bones and spine are attacked most often Recovery usually is satisfactory unless the bone itself is involved as an osteitis Recurrence is common Typhoid bacilli residing in the lymphoid marrow cells presumably give rise to the condition They may be cultivated for years from the lesions and from the purulent discharges through draining sinuses Redness pain tenderness and swelling over the affected area together with roentgenographic evidence establishes the diagnosis The condition should be suspected and sought whenever pain in bones is present

Rare Occurrences and Complications — Agranulocytosis encephalomyelitis tonsillitis subcutaneous and mediastinal emphysema hemiplegia and noma have occurred *The blood may be invaded by staphylococci or hemolytic and non* hemolytic streptococci Typhoid and paratyphoid bacilli both may be present Typhoid may coexist with brucellosis syphilis malaria tuberculosis bacillary dysentery amebic dysentery cholera and other diseases

Typhoid and Pregnancy — A patient may pass safely through an attack of

tion of severe typhoid, and death is due either to uremia or to general intoxication or to both After recovery from typhoid the urine returns to normal within a month or two When recovery occurs it is apparently complete Rarely does the nephritis become chronic

Pyelitis Pyelonephritis — These are more common than classical nephritis Chills or irregular temperature with pain and tenderness in the lumbar region hematuria pyuria and bacilluria are suggestive of pyelitis or pyelonephritis which almost always occur together Pyelitis may be caused by typhoid bacilli or other bacteria Symptoms of pyelonephritis may dominate those of systemic typhoid[31] The prognosis is good when modern therapy is used

Cystitis — Cystitis as a complication occurred in 2 1 per cent of the Johns Hopkins Hospital series It is usually due to the typhoid bacillus When it follows catheterization pyogenic cocci or colon bacilli may be responsible The symptomatology does not present any special features When due to the typhoid bacillus the recovery usually is rapid and complete Other forms may be persistent Cystitis usually develops late in the course of the disease and is more frequent in those patients who have had retention of urine, obstruction or other abnormality The symptoms and signs are chills, sweats pain over the bladder, pain on urination frequency of urination and purulent or bloody urine

Spleen — Rupture of the spleen and abscess of the spleen both are rare occurrences Rupture of the spleen rarely is diagnosed during life as the profuse hemorrhage usually is quickly fatal A sudden severe pain in the splenic region with evidence of great loss of blood and presence of dulness in the left flank are suggestive signs and symptoms Abscess of the spleen may give rise to a few symptoms or there may be chills sweats leucocytosis and pain in the splenic region *In case of associated perisplenitis a friction rub may be heard* Diaphragmatic pleurisy may occur

Eye — Serious lesions of the eye are rare Temporary paralysis of the extrinsic eye muscles of unknown cause may develop during convalescence When optic neuritis develops, usually it is associated with meningitis Retinal hemorrhages are rare Transitory and permanent amaurosis has been reported At times this is due to nephritis in others intracranial disturbances are responsible Bilateral hemiopia has occurred

Ear — Temporarily impaired hearing is present in 4 per cent of patients Otitis media caused by pyogenic bacteria develops as a complication in about 2 per cent In stuporous patients it is well to bear in mind the importance of examination of the ears Furunculosis of the external canal is quite frequent Other unusual complications are hemorrhages into the cochlea and vestibule and cellular infiltration of the membranous labyrinth

Muscles — *Myositis* occurs Rupture of muscles with hematoma may occur and become secondarily infected as in other infectious diseases

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The onset may be sudden like an acute lumbago or there may be a gradually increasing pain especially noticeable on movement In addition to radiating around the trunk it may extend into the lower extremities At times the spine is held rigid and bending becomes impossible There may be tenderness and paresthesia along the thoracic or lumbar nerves and spasm of the muscles they supply Pressure on the spinal cord may cause disturbance of the reflexes and persistent weakness of the legs Muscular atrophy of the legs kyphosis or scoliosis may develop Disturbances of the bladder and rectum have been noted in a few instances

In spite of the intense pain and rigidity complete or almost complete recovery may be expected in a few weeks or months but in some cases one or more years may elapse before restoration occurs

Periostitis is the most common lesion of bones and as stated may appear during an attack but usually as a sequel sometimes not for months or years after the primary disease It occurs in about 1 per cent of patients The ribs clavicles long bones and spine are attacked most often Recovery usually is satisfactory unless the bone itself is involved as an osteitis Recurrence is common Typhoid bacilli residing in the lymphoid marrow cells presumably give rise to the condition They may be cultivated for years from the lesions and from the purulent discharges through draining sinuses Redness pain tenderness and swelling over the affected area together with roentgenographic evidence establishes the diagnosis The condition should be suspected and sought whenever pain in bones is present

Rare Occurrences and Complications — Agranulocytosis encephalomyelitis tonsillitis subcutaneous and mediastinal emphysema hemiplegia and noma have occurred The blood may be invaded by staphylococci or hemolytic and non hemolytic strepotococci Typhoid and paratyphoid bacilli both may be present Typhoid may coexist with brucellosis syphilis malaria tuberculosis bacillary dysentery amebic dysentery cholera and other diseases

Typhoid and Pregnancy — A patient may pass safely through an attack of

typhoid without interruption of pregnancy More frequently however, abortion or premature labor occurs Curschmann[1] reported on 36 cases Three of these went to term and were delivered during convalescence of a living child Fourteen passed through the typhoid without interruption of pregnancy The remaining 50 per cent miscarried, but only 3 died Others however, have reported less favorably No doubt the intensity of the attack, the condition of the patient and the stage of pregnancy are important factors in determining the frequency of miscarriage Sacquin collected statistics of 233 cases, 150 miscarried, and the mortality was 37 or 16 per cent

Clinical Pathology

Stools — There is nothing characteristic about the stools during typhoid They may be formed or diarrheal Occult blood often is present in the stages of necrosis and ulceration, if large vessels are eroded, the stools may consist largely or entirely of bright red blood, if passed soon after bleeding or they may be black and sticky if the blood has been retained for a time Typhoid bacilli may be present in 18 per cent of cases[41] early in the disease but more often, in 30 per cent from the second to the fifth week Their number is greatest high in the small intestine and they diminish toward the rectum

Urine — Febrile albuminuria in the nature of a transient nephrosis common to most febrile states is present almost always because of slight glomerular and tubular changes The urine often is concentrated and highly colored unless large amounts of fluid are ingested Casts pus and erythrocytes are uncommon except with nephritis or pyelonephritis Excessive hemolysis may cause hemoglobinuria Amino acids are excreted as a result of excessive destruction of tissue The diazo reaction once regarded as an important test, occurs in about 70 per cent of patients during the severe stages, but it is present in other infections as well Typhoid bacilli are rarely present in the first week but are present in from 5 to 30 per cent of patients in the later stages The renal function is not disturbed as a rule

Blood — In most patients especially in those with severe attacks a degree of secondary anemia develops On the average the erythrocyte count falls about 1 000 000 and the amount of hemoglobin is in proportion When hemorrhage occurs the count stays normal for a time until the volume of blood lost is replaced by fluid when there is evidence of anemia in proportion to the amount of bleeding and the degree of dilution

The average leucocyte count in typhoid is between 5 000 and 6 000 but counts may vary from 2 000 to 10 000 Leucopenia may persist throughout the disease and is no indication of severity of the disease nor of prognosis except in rare cases of granulopenia which may be fatal The number rarely exceeds

10 000 unless pyogenic complications occur The relative proportions of polymorphonuclear cells to lymphocytic ones is not disturbed significantly Toxic granules may be present Eosinophiles are present rarely

The proteins of the plasma especially the fibrinogen usually are diminished in severe cases late in the disease, consequently the sedimentation rate of erythrocytes is not increased as it is in many other infections The blood platelets usually are slightly diminished in number during the disease and increased in number afterward The prothrombin time is reduced slightly in amount The nonprotein nitrogen and urea nitrogen are not increased unless there is renal insufficiency

Bacteremia probably occurs early in all cases but is demonstrable by blood culture in 78 per cent [41] in the first week The percentage would no doubt be higher if cultures were made more frequently The percentage of positive cultures diminishes later as follows second week 60 per cent third and fourth week 55 per cent fifth week 37 per cent and sixth week 14 per cent (See also Fig)

Specific Agglutinins —The Gruber Widal test depends upon the development of specific agglutinins in the blood for typhoid and paratyphoid bacilli Agglutinins are evoked by an attack of the disease or by specific vaccination The reactions are specific in high dilution but cross reactions between typhoid or paratyphoid antigens do occur as a result of protein fractions common to each The presence of agglutinins indicates a degree of immunity to typhoid but not complete protection from infection Patients with high titer of agglutinins during the disease may die and those with none at all may recover The titer is of no value in prognosis In about 10 per cent of typhoid patients agglutinins are never demonstrable (see Fig 2)

Agglutinins begin to appear in significant titers that is over 1 80 about the tenth day of disease They may be present before the onset In some instances their appearance may be delayed for weeks and in others they never appear The titer as a rule continues to rise during the second and third weeks usually to 1 160 to 1 1 280 sometimes over 1 20 000 After reaching its strongest point the titer usually diminishes gradually and disappears after a few months Agglutinins may persist for years as a result of continued presence of typhoid bacilli in the body either as a chronic infection or in healthy carriers

Agglutinins appear in 90 per cent of persons vaccinated and reach their highest titer in the second or third week to disappear gradually in several months Agglutinins may persist at low titer for 1 to 2 years Protective antibodies sufficient to protect against ordinary exposure often are present also for 2 years or longer In vaccinated persons immune bodies may persist as long as 10 years According to Siler[7] increases in both flagellar (H) and of body (O) agglutinin constantly appear after vaccination the former in greater strength The

"O" or body agglutinin seems to be more closely related to specific immunity than the "H" antigen.

Agglutinins which are too weak to be demonstrable may become greatly increased by other infections as the so-called *anamnestic* or *recall reaction*. Typhoid likewise may evoke latent agglutinins in high titer for the causes of other diseases such as brucellosis or the Weil-Felix reaction of the rickettsial group. The complement fixation test for syphilis may be temporarily positive during typhoid.

The Widal reaction may appear in persons who have never been vaccinated against typhoid or have never knowingly had the disease, probably as the result of subclinical or inapparent infection.

Diagnosis

Diagnosis of typhoid in the earliest stages is often impossible unless an epidemic is present in the community, or there is some other reason to suspect it such as recent ingestion of food or water likely to be contaminated, swimming in contaminated water, caring for a patient with typhoid, handling cultures and so forth. Since the earliest symptoms and signs usually are mild and common to most infections, typhoid seldom is suspected until the symptoms and signs increase in intensity and are of the kind discussed on a previous page. The problem is even more difficult when the onset is uncharacteristic or if unusual symptoms are present. The ultimate proof of typhoid rests on recovering the bacillus, although it must be admitted that in some undoubted attacks bacilli may never be isolated despite energetic use of the recognized diagnostic procedures. Leucopenia or a normal number of leucocytes are important evidence.

In the first week bacteremia is almost always present and bacilli may be cultivated in as high as 90 per cent of cases. Blood, preferably in 10 c.c. amounts, should be transferred to appropriate media at daily intervals or every second or third day until bacteria are recovered. Cultures made of the sternal marrow are said to be positive as often as those made from the blood and may be positive, when those from the blood are sterile. According to H. C. Kao cultures of the marrow are positive more often than those of the blood. An example is illustrated in the legend of Fig. 7, in which case the marrow was the only source from which bacilli were recovered on the thirty-eighth day. Since typhoid bacilli are less often present in the feces and urine in the first week, cultures of both dejecta also should be made repeatedly. The Widal reaction is not evident early unless the patient has been previously vaccinated, especially during the previous year, or if he has had typhoid before. Agglutinins for other diseases may reappear. A precipitin reaction occurring when serum from a typhoid patient is overlaid on specific immune rabbit serum is proposed as a new test by Dennis and Saigh[1s0].

It is said to be positive often as early as the seventh day but a negative test does not exclude typhoid

Later in the disease clinical diagnosis is more reliable but attempts to isolate the bacillus must be continued The appearance of rose spots and persistent leucopenia or a normal number of leucocytes are important diagnostic factors The relative frequency with which bacilli may be recovered from the blood the feces and the urine is illustrated in Fig The Widal reaction often becomes demonstrable after the tenth day Blood for the Widal test may be withdrawn at the same time that the blood culture is made Dried blood also may be submitted for the test To be of diagnostic significance the titer must rise higher than 1 to 80 In making the test antigens for typhoid paratyphoid A paratyphoid B and in some instances for paratyphoid C should be used Cross reactions among the four strains occur at low dilution but usually as the disease progresses agglutinins for the infecting strain rise in higher titer than for the others All tests if negative must be repeated at appropriate intervals until proof is obtained According to Siler[7] diagnosis in 173 cases was confirmed as follows

Method	Number	Per Cent
Isolation of *E typhosa* from blood urine or feces singly or in combination	129	75
Agglutination tests showing increase in titer during course of disease	16	9
Positive necropsy findings	9	5
Clinical diagnosis based on signs symptoms and course of disease Laboratory findings negative or not done	19	11

Typhoid bacteremia together with clinical symptoms and signs proves a diagnosis but it must be remembered that carriers who shed typhoid bacilli in the feces and urine may suffer from some other disease not typhoid A positive Widal reaction may develop also during other diseases as discussed on a previous page

The isolation and identification of bacilli of the typhoid paratyphoid group require special bacteriological procedures All tests should be made by competent personnel

Differential Diagnosis

It is evident that typhoid in the earliest stage and often later has characteristics in common with many other infections All efforts must be made to establish etiological diagnosis as early as possible both for the sake of appropriate treatment and for proper epidemiological control

Among the diseases which are mistaken most often for typhoid in the early period are grip the common cold bronchitis influenza viral pneumonia infectious mononucleosis acute appendicitis measles typhus malaria dengue bacillary dysentery and kala azar Later in the course brucellosis subacute bacterial endocarditis septicemia with various bacteria especially the meningococcus

tuberculosis psittacosis ornithosis, trichinosis, malaria, tularemia, diseases of rickettsial origin kala azar and various forms of meningitis and encephalitis should be considered in making a diagnosis Most of the diseases mentioned are characterised by a gradual onset, fever and a normal or diminished number of circulating leucocytes Numerous others may be brought to mind especially when typhoid exhibits unusual manifestations Differential diagnosis rests on the evolution of signs, symptoms and clinical pathology of the diseases in mind the outcome of the disease epidemiological features specific serological or skin tests and chief of all the isolation of the causative agent all of which are discussed in detail in respective appropriate places in other chapters of Oxford Medicine A few important points may be mentioned briefly here

In the author s recent experience the viral pneumonias may exactly mimic typhoid at times except for the later predominance of pulmonary involvement, sweating and occasional later appearance of a cold agglutinin in the blood Pneumonias of the psittacosis ornithosis group may be identified positively by isolating the causative organisms and tentatively by the development of group specific complement fixing antibodies and by epidemiological factors Measles is recognized by coryza the evolution of the eruption and Koplik spots, subacute bacterial endocarditis by previous history of rheumatic fever, cardiac lesions the clinical course and by the isolation of the causative streptococcus, brucellosis by the epidemiological evidence lymphocytosis specific agglutinin skin test and cultural procedures tuberculosis by the previous history of contact or of disease, roentgenographic evidence a rapid pulse rate and sedimentation rate and the demonstration of *M tuberculosis* trichinosis by the history of ingesting infected pork, pains in the muscles eosinophilia and the demonstration of the larvas Tularemia, especially the "typhoid form", endemic typhus Rocky Mountain spotted fever and other rickettsial diseases may be recognized by epidemiological features evidence of insect bites specific serological reactions and the isolation of the etiological agents

In parts of the world where malaria dengue epidemic typhus, kala azar and other parasitic diseases are present differentiation often is difficult In malaria, when parasites cannot be found a therapeutic test with specific drugs may be helpful The outstanding features of kala azar are the anemia bleeding severe leucopenia greatly enlarged soft spleen hyperglobulinemia the presence of leishmania in blood culture or in smears and cultures from the bone marrow and spleen and the therapeutic effect of antimony compounds

Prognosis

Duration — Mild attacks may last a few days to a week or more The average duration of the more severe forms is from 3 to 5 weeks Curschmann s

statistics of 50 years ago may be compared with those of a maller series of cases reported in 1928[41] as follows

	Curschmann	Zia
Up to three weeks	57 per cent	25 per cent
Three to five weeks	32 per cent	39 per cent
More than five weeks	11 per cent	36 per cent

The duration in Curschmann s series measured from the onset of disease to the end of convalescence averaged 55 days The author has observed an attack lasting 9 months

According to the table the average duration is longer now than in the past but it is likely that the difference is really not so great and may be explained partly by different criteria applied by the two men Statistics of both duration and mortality no doubt have been modified in modern times by improved methods of diagnosis of typhoid and by the exclusion of other diseases which now are recognized correctly by laboratory methods but which formerly were diagnosed as typhoid

Death Rate — The death rate varies according to observers in different parts of the world who survey different classes of patients In general it is reported as between 5 and 20 per cent In an outbreak of 60 reported attacks in Philadelphia in 1945 8 deaths occurred or 13 per cent It is probably lower considering the number of unrecognized mild attacks not included in the statistics Furthermore statistics usually emanate from hospitals where patients with the severest attacks are sent Patients with mild attacks stay home and may not even seek medical aid

In an epidemic studied in Ohio in 1920 the death rate was 2 8 per cent (Christian) Prophylactic vaccine has no effect on the death rate of those who subsequently contract typhoid The mortality rate of the paratyphoid fevers *is lower than that of typhoid*

The mortality rate is the same in all races and in either sex The rate is especially high in infants under _ in aged persons in persons subject to starvation exposure debilitation obesity preexisting chronic disease and in those with concurrent or intercurrent infections of other cause However the death rate may be high in those in previous apparent robust health Persons between the ages of and 15 resist the disease best

Causes of Death — Toxemia and/or circulatory collapse account for about half of the deaths in typhoid Perforation causes about 15 per cent of deaths and hemorrhage about 10 per cent Pulmonary or renal involvement intercurrent infections elsewhere emboli and other occurrences and complications account for the rest Unfavorable symptoms are hyperpyrexia persistent tachycardia evere toxemia paralytic ileus and coma Sudden death may occur for no discoverable reason during the disease or in convalescence

tuberculosis, psittacosis ornithosis, trichinosis, malaria tularemia diseases of rickettsial origin kala azar and various forms of meningitis and encephalitis should be considered in making a diagnosis Most of the diseases mentioned are characterised by a gradual onset, fever and a normal or diminished number of circulating leucocytes Numerous others may be brought to mind especially when typhoid exhibits unusual manifestations Differential diagnosis rests on the evolution of signs, symptoms and clinical pathology of the diseases in mind, the outcome of the disease epidemiological features, specific serological or skin tests and chief of all the isolation of the causative agent, all of which are discussed in detail in respective, appropriate places in other chapters of Oxford Medicine A few important points may be mentioned briefly here

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Prognosis

Duration —Mild attacks may last a few days to a week or more The average duration of the more severe forms is from 3 to 5 weeks Curschmann s

travel in localities where the food and water supply may be unsafe or where typhoid is endemic or epidemic As large a percentage of the population as possible should be vaccinated during calamities like war flood or earthquake when the control of food and water supply is interrupted Laboratory workers especially should be protected

Antityphoid vaccination although it reduces the risk from occasional contact infection may be much less effective when vaccinated persons are submitted to severe or continuous infection

Antityphoid vaccination properly conducted reduces the incidence in general from 4 to 6 times Vaccination is a preventive measure of major importance when persons living in an uninfected area migrate to a place where typhoid is endemic and adequate sanitary procedures including the control of carriers would reduce typhoid to a point where there would be no need for vaccination in those who stay at home[25]

Persons vaccinated against typhoid are apt to become overconfident of its value and enjoy a false sense of security Vaccinated persons must be instructed to take no more chances of becoming infected than those who are not vaccinated

Personal Prophylaxis — In average daily life in American cities where the rules of sanitation are observed the risk of contracting typhoid fever is small except of course in the proximity of a carrier The risk of infection is greater when there are patients with typhoid in the community As little contact as possible should be had with patients or with infected materials The hands should be scrubbed after each exposure and especially before meals Gowns and rubber gloves are protective when worn in the sick room but are hardly necessary The disease can be avoided if precautions are taken to obtain uncontaminated food and water If contamination is suspected all food and beverages must be sterilized Contamination may occur after sterilization The practice of eating and drinking only hot food during an outbreak is wise Vegetables fertilized with human excrement are dangerous as are vegetables or fruit washed or sprayed with polluted water Native servants and cooks must be supervised rigidly in parts of the world where primitive sanitation exists In epidemic times it is unwise to indulge in any excesses particularly with food and alcoholic drink or to become unduly fatigued Bathing or swimming in polluted water is dangerous The question of antityphoid paratyphoid vaccination has been mentioned already and the discussion is continued in the next section

Prophylactic Vaccination

Vaccination with freshly isolated heat killed virulent smooth colony bacilli of the typhoid group affords a degree of specific protection against infection with moderate numbers of the respective bacilli in most but not in all instances

Prophylaxis

General Measures — The prevention of typhoid depends on the application of knowledge as discussed under Epidemiology Improvement of the standard of living and all that it implies and the dissemination of knowledge automatically aid in the control of typhoid Modern building construction controlled water and food supply refrigeration pasteurization, plumbing, sewage disposal, insect control and vaccine have all contributed to reducing the incidence of typhoid fever As in certain other infectious diseases prevention is much more easily accomplished than successful treatment

Of prime importance is the elimination or control of the sources of infection as found in patients with the disease or in carriers Both should be sought by trained officers and should be isolated preferably in hospitals Carriers must be prohibited from handling food and beverages for others They must be instructed and obliged to observe the rules of personal hygiene, especially of washing the hands after defecation Patients utensils clothing and bedding should be sterilized by washing in soap and hot water, by heat or by chemicals Thermometers must be washed and kept in 70 per cent solution of ethyl alcohol Their urine vomitus and finely broken up feces should be mixed with equal amounts of 1 1 000 bichloride of mercury solution, with 10 per cent formalin or with 3 per cent bleaching powder and allowed to stand several hours before disposal in sewers or in deep covered pits Privies should be built and located away from a water supply Bed pans and urinals should be sterilized with live steam boiling water or with bichloride of mercury solution Enema tubes and catheters need sterilization with soap and water and immersion in 70 per cent alcohol or 1 1 000 mercury bichloride solution The hands of attendants should be scrubbed thoroughly with soap and hot water after coming in contact with the patients or with soiled articles Water used for drinking must be uncontaminated or sterilized by filtration by boiling or with chemicals Food and drink suspected to have been contaminated should be sterilized by cooking or pasteurization Flies and crawling insects must be eradicated by preparations of DDT and pyrethrum or screened from food and from fecal matter Rats and mice should be destroyed with sodium fluoroacetate or by trapping Oysters and sea foods should not be eaten if fished from polluted water

When an epidemic exists or is imminent general information given in simple language telling what to do to avoid infection should be broadcast by newspapers radio billboards posters handbills and public speakers

Mass vaccination of groups of persons exposed, or likely to be exposed to typhoid paratyphoid such as in military organizations camps and institutional groups is advisable but vaccination alone has never controlled endemic or epidemic typhoid It is wise to vaccinate all persons contemplating vacation or

developed typhoid 3 weeks after vaccination In the British Army[5] 80 attacks occurred among a group of 230 soldiers all of whom had had 3 yearly vaccinations the last injection in most patients had been given six months before It was supposed that massive infection had occurred in this group since no other similar outbreaks had been reported in the British Army

Method of Vaccination — Initial vaccinations should be made subcutaneously re-immunization may be made intracutaneously as described later Vaccination by the oral route is of little or no value Vaccine should conform to the U S P requirement and contain one billion typhoid bacilli and one half billion of para typhoid A and B bacilli each per c c

The vaccine is administered subcutaneously The first dose for an adult is 0 5 c c followed by 2 subsequent injections of 1 c c at 7 to 10-day intervals The site of injection most often used is over the insertion of the deltoid muscle on the left arm Transient redness soreness swelling and aching usually occur at the site of injection and adjacent lymph nodes which may last a day or two A constitutional reaction consisting of a chill or chilliness fever malaise anorexia general aching and headache may occur during the following 12 to 24 hours The most desirable time of vaccination is in the late afternoon and it is wise to avoid fatigue for the rest of the day The discomfort if present may be relieved by 0 3 gm (gr 5) doses of acetylsalicylic acid or by aminopyrine 0 18 gm (gr 3) repeated as required More severe immediate reactions which rarely occur may be controlled with the hypodermic injection of 0 5 c c of adrenalin solution Reactions cannot be predicted and no preliminary treatment has any influence in preventing them In any given person none of the injections each of the injections or any of the injections may be followed by discomfort

For re immunization in 2 or 3 years or sooner according to the need vaccine should be given 0 1 c c intracutaneously or 0 5 c c subcutaneously The former is preferable[7] since it rarely causes local or constitutional symptoms The intracutaneous route for the same reason is preferable in infants in the aged or in other circumstances in which reaction may be dangerous

Treatment

The discovery of the effectiveness of chloromycetin or chloramphenicol in typhoid has revolutionized its treatment The shortening of the disease to several days and the elimination of serious complications if maintained in the future will render unnecessary much of the detailed discussion of therapy about to be presented

As soon as typhoid is suspected the patient should be isolated and the local Health Officer notified The source of infection must be sought Persons who have been in immediate contact with the patient should be

Antibodies demonstrable as protective substances and specific agglutinins are stimulated Agglutinins for typhoid bacilli appear in the blood of most vaccinated persons after the second injection, reach their highest titer about 2 weeks after the last injection and diminish gradually during the following months The average titer ranges between 1 160 and 1 320 but may reach 1 20 000 In a small proportion of persons no agglutinins appear The presence of agglutinins or the strength of their titer is only a rough indication of the existence of immunity but at present aside from the mouse protection test, it is the only available measure of immunity Experimental studies have shown that agglutinins are never present except in serum containing protective antibodies The immunity, which is evoked, is relative and not complete It may be broken through by a massive dose of infecting bacilli, and it may be reduced by other intercurrent infections or conditions Vaccine injected after the onset of symptoms has no specific effect on the disease Opinion differs as to its effect, if given shortly before infection according to some it provokes the attack sooner, and to others it may shorten the course The immunity derived from vaccination generally lasts from 1 to 3 years, although variation occurs Vaccination should, therefore, be repeated every 3 years or oftener if evident exposure occurs

Vaccine to be effective must be prepared with the bacilli likely to cause infection For example vaccine made with *E typhosa* alone will not protect against infection caused by paratyphoid bacilli Because of the low incidence of paratyphoid fever in the United States bacilli of the paratyphoid A and B were omitted from the vaccine used by the U S Army in 1934 but were restored in 1940 prior to sending troops to parts of the world where these infections are more common

Vaccination is contraindicated in the presence of other infections especially tuberculosis and chronic illness, because of the possible harmful effect of a reaction The author however has vaccinated a number of patients with nephritis and diabetes without untoward effects Vaccination of such patients evokes agglutinins of low titer or none at all When the use of vaccine is imperative in such instances it should be given intracutaneously rather than subcutaneously Several cases of acute neutropenia apparently caused by antityphoid vaccination are on record

Typhoid in Vaccinated Persons —Numerous reports of the development of typhoid in its usual severity and with its usual death rate in persons supposedly properly immunized by vaccine a short time previously cast doubt on the value of the procedure It is known however that vaccine does not protect all persons, and infection may occur if a large enough inoculum is ingested if too long a period elapses after vaccination if the vaccine is impotent, and if good vaccine is given improperly According to Siler[7] of 209 persons with typhoid, 53 per cent presumably had been immunized with vaccine within 3 years, and 13 per cent

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As soon as typhoid is suspected the patient should be isolated and the local Health Officer notified The source of infection must be sought Persons who have been in immediate contact with the patient should be

vaccinated and their stools studied bacteriologically to detect carriers All patients regardless of the early mildness or severity of the attack must have their blood typed , and suitable blood for transfusion must be available for use in blood banks or in matched donors It is wise also to have the services of a surgeon conveniently at hand in case of need In general typhoid is best managed in a hospital with adequate facilities for laboratory tests and therapeutic procedures and where prompt aid is ready in case serious occurrences or complications arise If the patient is treated at home one or more trained nurses should be engaged to provide continuous day and night nursing service Attendants employed to care for the patient should be vaccinated or otherwise immune They must be instructed in regard to special hygienic measures All data such as temperature pulse and respiration rates blood pressure blood counts laboratory studies intake and output medication and any unusual occurrences should be observed measured and accurately recorded on the usual hospital chart forms

Treatment concerns (a) the use of chloromycetin or chloramphenicol (b) competent nursing care (c) symptomatic therapy (d) proper nutrition (e) detection and treatment of serious occurrences or complications (f) management of convalescence and (g) prevention of the spread of infection to others

Specific Therapy

Chloramphenicol (Chloromycetin) — Chloromycetin and its synthetic equivalent chloramphenicol administered in adequate amounts causes the fever to disappear by lysis during the first 3 or 4 days of treatment[33, 4, 41] An initial dose of 3 to 4 gm is followed by 1 to 3 gm daily in divided doses orally for 8 days or more depending upon the severity of the disease the response and other determining features Therapy for shorter periods is likely to be followed by relapse There is little reason to continue treatment longer than 14 days Serious toxic effects of the drug have not been reported In several patients treated less than 8 days relapse occurred with intestinal hemorrhage and perforation[11]

While both streptomycin and aureomycin inhibit the growth of *S typhosa* in cultures they have little or no influence of the disease Penicillin or the sulfonamide drugs are of no value[3]

Typhoid vaccine has no logical basis for use in therapy and should not be used The foreign protein shock reaction which results from the

injection of any vaccine or protein occasionally terminates the disease but it may be harmful or fatal and is not recommended Numerous attempts to develop an effective specific antiserum thus far have been unsuccessful Bacteriophage therapy has not been found to influence the course of the disease

Nursing Care

The patient should be put to bed promptly and kept there until well into convalescence The patient should be disturbed as little as possible and only when actual need arises The sick room should be light well ventilated and comfortable with convenient bathroom facilities The windows should be screened in the warm months The mattress and pillows must be smooth and comfortable to avoid bed sores during a long illness The bed pan must be used It is wise to place a rubber sheet under the linen to prevent soiling the mattress with excreta Excreta must be treated and disposed of as outlined under Prophylaxis The patient must be watched at all times to detect hemorrhage perforation or other complications and especially if delirious to prevent escape from bed and injury to himself or others Oral hygiene is important to avoid sordes stomatitis and parotitis Alkaline mouth washes or dilute hydrogen peroxide may be used once or twice daily The teeth and gums should be brushed regularly Mouth swabs may be used in uncooperative patients Cold cream or 10 per cent glycerin solution frequently applied to the lips prevents drying and cracking A daily sponge bath with tepid soapy water rinsing and thorough drying is recommended An alcohol rub and subsequent dusting with talcum powder provides comfort Attendants should be instructed in regard to the symptoms and signs of hemorrhage or perforation and ordered to report any significant evidence or unusual occurrences immediately to the physician

Symptomatic Treatment

The bowels should be kept open with small enemas of plain water at least every other day if necessary Liquid petrolatum 15 c c (½ ounce) by mouth may be given daily Mild laxatives usually are contraindicated but may at times be used to initiate movement Cathartics are dangerous and may cause hemorrhage and perforation Constipation and

vaccinated and their stools studied bacteriologically to detect carriers All patients regardless of the early mildness or severity of the attack must have their blood typed, and suitable blood for transfusion must be available for use in blood banks or in matched donors It is wise also to have the services of a surgeon conveniently at hand in case of need In general typhoid is best managed in a hospital with adequate facilities for laboratory tests and therapeutic procedures and where prompt aid is ready in case serious occurrences or complications arise If the patient is treated at home one or more trained nurses should be engaged to provide continuous day and night nursing service Attendants employed to care for the patient should be vaccinated or otherwise immune They must be instructed in regard to special hygienic measures All data such as temperature pulse and respiration rates blood pressure blood counts laboratory studies intake and output medication and any unusual occurrences should be observed measured and accurately recorded on the usual hospital chart forms

Treatment concerns (a) the use of chloromycetin or chloramphenicol (b) competent nursing care (c) symptomatic therapy (d) proper nutrition (e) detection and treatment of serious occurrences or complications (f) management of convalescence and (g) prevention of the spread of infection to others

Specific Therapy

Chloramphenicol (Chloromycetin) —Chloromycetin and its synthetic equivalent chloramphenicol administered in adequate amounts causes the fever to disappear by lysis during the first 3 or 4 days of treatment[43, 48, 44] An initial dose of 3 to 4 gm is followed by 1 to 3 gm daily in divided doses orally for 8 days or more depending upon the severity of the disease the response and other determining features Therapy for shorter periods is likely to be followed by relapse There is little reason to continue treatment longer than 14 days Serious toxic effects of the drug have not been reported In several patients treated less than 8 days relapse occurred with intestinal hemorrhage and perforation[11]

While both streptomycin and aureomycin inhibit the growth of *S typhosa* in cultures they have little or no influence of the disease Penicillin or the sulfonamide drugs are of no value[3]

Typhoid vaccine has no logical basis for use in therapy and should not be used The foreign protein shock reaction which results from the

Headache — For severe headache the usual analgesic drugs may be given for short periods but not continued An ice cap or cold cloth to the head is comforting Aspirin 0 3 to 0 6 gm (gr 50 to 10), or amidopyrine, 0 18 to 0 3 gm (gr 3 to 5), may be given for 1 or 2 doses at times

Circulatory System — Circulatory failure and a shocklike condition occurs and may be confused with the symptoms of hemorrhage or perforation The conditions mentioned require speedy and careful clinical differentiation Differentiation must be made between various causes of circulatory failure one as a result of peripheral collapse of the vasomotor system and the other from heart failure itself because the treatment of each is different The conditions come without warning They may be mild or severe they may be repeated and they are important causes of death

In peripheral vasomotor collapse 1 000 c c of 5 per cent glucose in normal physiological salt solution should be given immediately by the slow intravenous drip method to be replaced by the injection of 3- gm of lyophilized plasma or 500 c c of normal plasma as soon as it is available Lyophilized plasma may be diluted to normal concentration or may be doubled in strength by using half the amount of diluent of triple distilled water The intraosseous preferably the sternal route of injection may be used if the veins are inaccessible or collapsed If the patient is anemic 50 c c to 500 c c of whole blood may be used The body temperature should be maintained near 37 C (98 6 F) by warm blankets hot water bottles and an electric pad Oxygen may be helpful for cyanosis and dyspnea Therapy often is ineffectual

If evidence of sudden heart failure and pulmonary edema occur *phlebotomy* of 250 to 500 c c of blood and rapid digitalization are needed together with maintenance of normal temperature and the administration of oxygen Morphine sulfate 15 mgm (gr ¼) is needed for apprehension and restlessness The various so-called cardiac stimulants such as coramine camphor strychnine caffeine and others should not be used Atropine is of no value and may even be dangerous

Fluid and Diet

Fluid should be offered freely so that from 1 000 to 3 000 c c (1 to 3 quarts) a day are taken If necessary it may be given subcutaneously

abdominal distention often can be avoided by providing a proper diet to cause a soft stool

Diarrhea seldom is troublesome and if it occurs can often be relieved by changing the diet If necessary powdered opium 0 06 gm (gr 1) with bismuth subcarbonate 1 gm (gr 15), or chalk mixture, 15 to 30 c c (½ to 1 ounce) may be given every 2 or 3 hours until the desired effect is obtained Camphorated tincture of opium (paregoric), 1 c c (15 minims), every 3 hours may be used Heat may be applied to the abdomen

Abdominal Distention — When distention does occur it is treated by changing the diet or by reducing the amount of milk sugar or protein in it It is necessary to experiment somewhat until a suitable combination is arranged An enema or the insertion of a rectal tube may aid in the expulsion of gas Passage of a tube into the stomach or small intestine and suction may be helpful Drinking carbonated water may help to raise the gas The application of hot turpentine stupes to the abdomen is a time honored remedy of doubtful efficacy The same effect of counter-irritation can be obtained more simply with a hot water bottle or an electric pad The same may be said for turpentine or other medicated enemas plain warm water is just as effective Some observers record success with the subcutaneous injection of pituitrin and of prostigmine but because of the resulting intestinal contractions the danger of perforation or hemorrhage must be borne in mind

Fever — Unless the temperature exceeds 40° C (104° F) it is seldom necessary to employ means to reduce it unless delirium is present The most desirable form of antipyretic hydrotherapy is the tepid or cool sponge bath Hydrotherapy should be continued only if the desired effect is obtained and stopped if the patient objects or becomes exhausted Antipyretic drugs are not recommended For insomnia restlessness or apprehension various drugs of the barbital group may be used judiciously for short periods

Delirium if mild often can be controlled by persuasion and dissuasion In patients not easily controlled it may become necessary to administer sedative drugs such as sodium bromide 1 gm (gr 15), phenobarbital 0 03 to 0 18 gm (gr ½ to 3) or sodium amytal 0 2 gm (gr 3) repeated at intervals if necessary Paraldehyde morphine or hyoscine are used only for periods of extreme excitement or mania Under certain conditions a restraining sheet or anklets fastened to the bed may be needed A cool sponge bath may be helpful

Hemorrhage

Bleeding from the bowel sufficient to be recognized either symptomatically or by the passage of bloody or black stools requires careful management It is recommended that the patient be kept absolutely quiet with the assistance of hypodermic injections of morphine in 10 to 15 mgm (gr 1/6 to 1/4) doses at intervals as required If morphine is used the question of masking the symptoms of possible perforation and the danger of causing distention must be kept in mind Food by mouth should be withheld for at least a day Water in small amounts is allowed An ice bag often is placed on the abdomen but it is doubtful what good it can do except to keep the patient quiet Bowel movements should be passed on a large absorbent pad to avoid the exertion of using a bed pan The amount of hemoglobin red blood cell count and blood pressure should be observed at hourly or longer intervals When the bleeding has been profuse and the anemia profound blood transfusion should be performed It requires good judgment to know when to inject blood at what rate it should flow and how much to give The shock like state and low blood pressure which often follows massive hemorrhage is a natural way to stop bleeding and a short period of waiting may give the patient time to recuperate spontaneously In general however when there is sudden loss of a large amount of blood transfusion is necessary Under the circumstances it is preferable to give 250 to 500 c c of matched whole blood or of plasma intravenously at a fairly rapid rate of 20 to 40 c c a minute until the blood pressure rises somewhat but not necessarily to normal The amount needed varies according to the amount of blood lost the cessation or continuation of bleeding and the response of the patient Too much blood should not be injected too quickly so that the blood pressure does not rise high enough to cause bleeding to persist Ordinarily the slow intravenous drip method is used The intraosseus (sternal or tibial) route of injection may be used if veins are inaccessible

No drugs given either by mouth or parenterally have proved to be of value in controlling hemorrhage Although no studies on the subject have been reported it is probable that because of the possible interference with function of the liver vitamin K may be of value if given prophylactically to prevent bleeding or even after bleeding has begun Doses of 2 to 5 mgm daily of vitamin K given subcutaneously may be tried Treatment may be continued for a week or two

When the hemorrhage has stopped it is wise not to move the bowels for a day or two Feeding may be resumed gradually

as physiological salt solution or 5 per cent glucose or intravenously or intraosseously in stronger concentration of glucose to supply the requisite number of calories. Orally or parenterally administered amino acids are of value.

Unless a full diet is maintained, loss of weight and anemia will appear in a prolonged disease like typhoid. The average patient needs a suitable diet of approximately 3,000 calories, less or more according to body weight. Adequate diet prevents constipation and tympanites. Food should be prepared attractively and served according to the patient's desire as far as possible. Frequent small feedings of soft, easily digestible foods should be offered. Lactose is superior to cane sugar and as much as 100 grams (3 ounces) may be added to a glass of lemonade. Carbohydrates may be supplied also as candy, jelly, strained honey and sweetened fruit juices. Butter, cream and ice cream will furnish protein. Vegetable purees, mashed or baked potato, toast or crackers are allowed. Beverages may include fruit juices, carbonated water, ginger ale or beer. Brandy or whiskey in 15 to 30 c c (½ to 1 ounce) doses may be given 3 or 4 times a day if agreeable to the patient. As mentioned above under certain conditions it may be necessary to supply nutriment intravenously as amino acids and dextrose solution.

A sample of a suitable 3,000 calory diet is listed here. Various modifications or additions may be made as necessary.

8 A M — Farina or other wheat or oat gruel, farina ¾ cup, milk ½ cup, cream ¼ cup, salt, toast 1 slice, butter 1 tablespoonful
10 A M — Cocoa 1 cup
12 NOON — Milk toast, milk ½ cup, cream ¼ cup, toast 1 slice, cream of pea soup 1 cup, egg 1, blanc-mange plain or flavored, ¾ cup, butter 2 tablespoonfuls
2 P M — Malted milk 1 cup
4 P M — Orangeade 1 glass
6 P M — Farina gruel 1 cup, milk ½ cup, toast 1 slice, butter 1¼ table spoonfuls, egg 1, cup custard ¼ cup
8 P M — Eggnog, plain or flavored, 1 glass

Vitamins may be supplied by giving thiamin hydrochloride 2 mgm, ascorbic acid 50 mgm and nicotinic acid 15 mgm daily.

For severe anemia with erythrocytes fewer than three million per cu mm transfusion of blood is advised.

merely be kept clean with dry sterile loose dressings Ointments macerate the skin and should not be used If infection with pyogenic bacteria is present penicillin parenterally or locally may be used

Convalescence

Although relapses may occur for no apparent reason generally they are provoked by indiscretions in diet exertion excitement and perhaps by other mild intercurrent infection It is wise therefore to keep the patient bedfast for at least a week or preferably two weeks after the temperature reaches normal Because of the variation in the severity of the disease and of the different speeds of recuperation of different patients the rules must be modified to suit individual behavior It is always better to be too cautious than too daring Hemorrhage perforation circulatory failure embolism and other dangerous sequels may occur during convalescence

According to the progress made exercise is increased gradually during the first week sitting up in bed during the second week and getting out of bed is permitted later The diet list and quantity is increased slowly according to desire of the patient The patient's weight should be measured and recorded twice a week The pulse rate may be abnormally fast or slow for several weeks but requires no special medication Mental depression and asthenia may be troublesome Anemia if present should be treated by appropriate measures as described elsewhere in these volumes If financial conditions permit a month's stay in a vacation place is desirable

Before a patient is released from supervision 3 samples of stools and urine taken at weekly intervals should be cultured for typhoid paratyphoid bacilli If present the patient must be regarded as a carrier

Treatment of Carriers

The treatment of carriers is unsatisfactory Since typhoid bacilli often reside in the gallbladder cholecystectomy is recommended by many[11, 13] The results therefrom as far as eliminating typhoid bacilli from the stool are concerned frequently are unsuccessful Cure by operation is never certain Even if bacilli are present in the bile obtained by intubation and aspiration there is no way of knowing whether the source

Perforation

This accident is a surgical problem and demands prompt repair Closure of the tear offers the only hope of recovery When diagnosis is not absolutely certain it is wiser to operate and be mistaken than to delay and permit the development of peritonitis The mortality rate in the latter case is nearly 100 per cent Operation and repair usually reduce the rate to 65 or 75 per cent No patient with perforation is too desperately ill to be operated upon

Various Complications

Cholecystitis — Cholecystitis, which accompanies typhoid, usually subsides spontaneously Hot applications may give relief from pain, morphine should not be used except in rare instances If evidence of obstruction develops, surgical consultation should be requested and drainage considered

Phlebitis — Phlebitis during typhoid is treated as usual The affected limb is immobilized and elevated with pillows and heat applied in the form of moist dressings soaked in water at about 37 8 C (100 F) for several days The amount or degree of activity allowed in respect to the danger of loosening emboli is a matter of judgment and chance Ligation at the groin level is advised by many

Bone Lesions — The treatment of typhoid arthritis periostitis and osteitis is a problem for an orthopedic surgeon Mild non suppurative lesions may heal spontaneously and the pain often can be relieved by immobilization with splints and the application of heat Suppurative lesions require drainage and surgical care

Pyelonephritis, pyelitis and *cystitis* caused by typhoid bacilli should be treated with streptomycin administered parenterally in doses of 1 to 4 gm daily since the drug is excreted in the urine in bactericidal amounts Chloromycetin or aureomycin may prove to be more effective

Complications caused by pyogenic bacteria such as staphylococci hemolytic streptococci and pneumococci whether they give rise to abscesses septicemia erysipelas pneumonia or other lesions require therapy with penicillin as described in appropriate places in these volumes

Bed-sores, which may develop despite the best of care should be treated by appropriate posture in bed by exposure to air and should

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of bacilli is solely in the gallbladder or elsewhere in the biliary tract or intestinal tract as well. Many surgical reports claiming success have not been controlled by prolonged and frequent examination of the stool. Carriers may shed typhoid bacilli at prolonged intermittent periods and examinations made during free periods give misleading information. Repeated examination should be made at monthly intervals for at least 1 year before cure can be said to be reasonably certain. The chances for cure by cholecystectomy are greater if symptoms of gallbladder disease are present, and if there is actual disease of the gallbladder with or without stones. Antityphoid vaccination has been recommended but has not been attended with success. Various so called intestinal and urinary antiseptics are useless[7]. The sulfonamide compounds including sulfaguanidine and sulfasuxidine have no effect on the carrier state according to some investigators[37] and are of value according to others. Studies are in progress at present on the subject. Streptomycin and aureomycin cleared the stools in a few treated patients while the drug was given orally but cultures of stools became positive again for *E. typhosa* soon after treatment was stopped[3]. Chloromycetin or chloramphenicol may be more effective. Antibiotics may be of more value in clearing the urinary tract of bacilli although no reports have appeared as yet on this phase of the subject.

Carriers should be informed as to their dangerousness in spreading disease and instructed in methods for the disinfection and safe disposal of their excreta and washing of hands after defecation. Carriers should never be permitted to handle foodstuffs or beverages. If rules are observed conscientiously they are of no danger in the average well-managed community. Carriers wilfully violating sanitary rules may require confinement in institutions for supervision.

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